

SUBSTITUTED BIPHENYL COMPOUNDS  
FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

5

This invention is in the field of anti-inflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG<sub>2</sub>, PGH<sub>2</sub> and PGE<sub>2</sub>, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

Substituted biphenyl compounds have been reported as components in photographic materials. U.S. Patent No. 5,238,790, to Shimura *et al.*, describes the use of biphenyl compounds as dispersion agents in photographic materials. U.S. Patent No. 5,294,530, to Seto *et al.*, describes photographic materials containing biphenyl compounds as anti-fading agents.

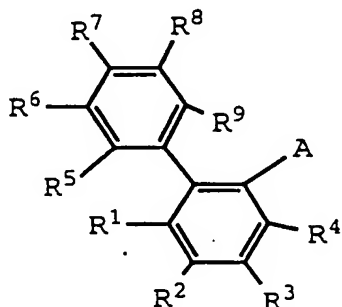
U.S. Patent No. 4,990,647, to Himmler *et al.*, describes a method for the preparation of unsymmetric biaryl compounds.

Substituted biphenyl compounds have been reported as having activity as angiotensin II antagonists. Heterocyclo-substituted biphenyl compounds are described by D. Kim, *et al.* [*Bioorg. Med. Chem. Lett.*, 4, 41-44 (1994)]. U.S. Patent No. 5,254,546, to Ardecky *et al.*, describes tetrazole substituted biphenyl compounds. U.S. Patent No. 5,240,928, to Allen *et al.*, describes aminosulfonyl-substituted biphenyl compounds.

Recently, a terphenyl compound has been described as an anti-inflammatory agent [R. Copeland *et al.*, *Med. Chem. Res.*, 5, 384-393 (1995)].

#### DESCRIPTION OF THE INVENTION

A class of compounds useful in treating inflammation-related disorders is defined by Formula I:



I

wherein A is selected from aryl and heteroaryl, wherein A is optionally substituted with one or more radicals selected from alkyl, halo, alkoxy, alkylthio, cyano, haloalkyl, amino, alkylamino, carboxyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, hydroxyl and mercapto; wherein each of R<sup>1</sup> through R<sup>4</sup> is independently selected from hydrido, halo, and alkoxy; and wherein each of R<sup>5</sup> through R<sup>9</sup> is independently selected from hydrido, alkyl, halo, alkoxy, alkylthio, cyano, haloalkyl, amino, alkylamino, haloalkoxy, hydroxyalkyl, alkoxyalkyl, hydroxyl, mercapto, aminosulfonyl and alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin-related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis,

multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The compounds would  
5 also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis, conjunctivitis, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with  
10 viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders such as Alzheimer's disease and dementia. The compounds of the invention are useful as anti-inflammatory agents, such as for the  
15 treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central  
20 nervous system damage resulting from stroke, ischemia and trauma.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of mammals, including companion animals and farm animals,  
25 such as, but not limited to, horses, dogs, cats, sheep and pigs.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatories, such as together with  
30 steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB<sub>4</sub> antagonists and LTA<sub>4</sub> hydrolase inhibitors.

Suitable LTB<sub>4</sub> inhibitors include, among others, ébselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound  
35 LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228,



calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB<sub>4</sub> inhibitors  
5 are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others,  
10 masoprocot, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over  
15 cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC<sub>50</sub> of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the  
20 compounds have a cyclooxygenase-1 IC<sub>50</sub> of greater than about 1 μM, and more preferably of greater than 10 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

25 A preferred class of compounds consists of those compounds of Formula I wherein A is selected from phenyl, naphthyl, 5-membered heteroaryl and 6-membered heteroaryl, wherein A is optionally substituted with one or more radicals selected from lower alkyl, halo,  
30 lower alkoxy, lower alkylthio, cyano, lower haloalkyl, amino, lower alkylamino, lower dialkylamino, lower haloalkoxy, lower hydroxyalkyl, lower alkoxyalkyl, Hydroxyl and mercapto; wherein each of R<sup>1</sup> through R<sup>4</sup> is independently selected from hydrido and halo; or  
35 wherein R<sup>2</sup> and R<sup>3</sup> together form -O(CH<sub>2</sub>)<sub>n</sub>O-; wherein n is 1 or 2, inclusive; and wherein each of R<sup>5</sup> through R<sup>9</sup> is independently selected from hydrido, lower

alkyl, halo, lower alkoxy, lower alkylthio, cyano, lower haloalkyl, amino, lower alkylamino, lower dialkylamino, lower haloalkoxy, lower hydroxyalkyl, lower alkoxyalkyl, hydroxyl, mercapto, aminosulfonyl  
5 and lower alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

A more preferred class of compounds consists of those compounds of Formula I wherein A is selected from phenyl, naphthyl, 5-membered heteroaryl and 6-  
10 membered heteroaryl, wherein A is optionally substituted with one or more radicals selected from lower alkyl, halo, lower alkoxy, lower haloalkyl and lower dialkylamino; wherein each of  $R^1$  through  $R^4$  is independently selected from hydrido and halo; or  
15 wherein  $R^2$  and  $R^3$  together form  $-O(CH_2)_nO-$ ; wherein  $n$  is 1 or 2, inclusive; wherein each of  $R^5$ ,  $R^6$ ,  $R^8$  and  $R^9$  is hydrido; and wherein  $R^7$  is selected from aminosulfonyl and lower alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

20 Within Formula I there is a subclass of compounds which consists of compounds wherein A is selected from phenyl, naphthyl, 5-membered heteroaryl and 6-membered heteroaryl, wherein A is optionally substituted with one or more radicals selected from  
25 lower alkyl, halo, lower alkoxy, lower haloalkyl and lower dialkylamino; wherein each of  $R^1$  through  $R^4$  is independently selected from hydrido and halo; or wherein  $R^2$  and  $R^3$  together form  $-OCH_2O-$ ; and wherein  $R^7$  is aminosulfonyl; or a pharmaceutically-acceptable  
30 salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein A is selected from phenyl, thienyl, furyl, pyrazolyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl,  
35 isothiazolyl, triazolyl and pyridyl, wherein A is optionally substituted with one or more radicals selected from methyl, ethyl, fluoro, chloro, bromo,

methoxy, ethoxy, propoxy, n-butoxy, methylenedioxy, ethylenedioxy, fluoromethyl, difluoromethyl, difluorochloromethyl, trifluoromethyl, dichloroethyl, dichlorofluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloropropyl, N-ethyl-N-methylamino, N,N-dimethylamino and N,N-diethylamino; wherein each of R<sup>1</sup> through R<sup>4</sup> is independently selected from hydrido, fluoro, chloro and bromo; or wherein R<sup>2</sup> and R<sup>3</sup> together form -OCH<sub>2</sub>O-; wherein R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> are hydrido; and wherein R<sup>7</sup> is aminosulfonyl; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a second subclass of compounds of high interest wherein A is selected from phenyl, naphthyl, 5-membered heteroaryl and 6-membered heteroaryl, wherein A is optionally substituted with one or more radicals selected from lower alkyl, halo, lower alkoxy, lower haloalkyl and lower dialkylamino; wherein each of R<sup>1</sup> through R<sup>4</sup> is independently selected from hydrido and halo; or wherein R<sup>2</sup> and R<sup>3</sup> together form -OCH<sub>2</sub>O-; and wherein R<sup>7</sup> is lower alkylsulfonyl; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula I wherein A is selected from phenyl, thienyl, furyl, pyrazolyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl and pyridyl, wherein A is optionally substituted with one or more radicals selected from methyl, ethyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, methylenedioxy, ethylenedioxy, fluoromethyl, difluoromethyl, difluorochloromethyl, trifluoromethyl, dichloroethyl, dichlorofluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloropropyl, N-

ethyl-N-methylamino, N,N-dimethylamino and N,N-diethylamino; wherein each of R<sup>1</sup> through R<sup>4</sup> is independently selected from hydrido, fluoro, chloro and bromo; or wherein R<sup>2</sup> and R<sup>3</sup> together form -OCH<sub>2</sub>O-; 5 wherein R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> are hydrido; and wherein R<sup>7</sup> is methylsulfonyl; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and 10 pharmaceutically-acceptable salts thereof as follows:

4-(2-biphenyl)benzenesulfonamide;  
4-[2-(3-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-methoxyphenyl)phenyl]benzenesulfonamide;  
15 4-[2-(3-fluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3-chlorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3-(N,N-  
dimethylamino)phenyl]phenyl]benzenesulfonamide;  
20 4-[2-(4-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,4-dimethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-methoxy-4-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-fluoro-4-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-chloro-4-methylphenyl)phenyl]benzenesulfonamide;  
25 4-[2-(4-methyl-3-  
trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3-(N,N-dimethylamino)-4-  
methylphenyl]phenyl]benzenesulfonamide;  
4-[2-(4-methoxyphenyl)phenyl]benzenesulfonamide;  
30 4-[2-(4-methoxy-3-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,4-dimethoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-chloro-4-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(4-methoxy-3-  
35 trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3-(N,N-dimethylamino)-4-  
methoxyphenyl]phenyl]benzenesulfonamide;

- 4-[2-(4-fluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(4-fluoro-3-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(4-fluoro-3-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,4-difluorophenyl)phenyl]benzenesulfonamide;  
5 4-[2-(3-chloro-4-fluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(4-fluoro-3-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3-(N,N-dimethylamino)-4-fluorophenyl]phenyl]benzenesulfonamide;  
10 4-[2-(4-chlorophenyl)phenyl]benzenesulfonamide;  
4-[2-(4-chloro-3-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(4-chloro-3-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(4-chloro-3-fluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3,4-dichlorophenyl)phenyl]benzenesulfonamide;  
15 4-[2-(4-chloro-3-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[4-chloro-3-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-(4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
20 4-[2-(3-methyl-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-methoxy-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-fluoro-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
25 4-[2-(3-chloro-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3,4-di(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
30 4-[2-[3-(N,N-dimethylamino)-4-trifluoromethylphenyl]phenyl]benzenesulfonamide;  
4-[2-[4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-[4-(N,N-dimethylamino)-3-methylphenyl]phenyl]benzenesulfonamide;  
35 4-[2-[4-(N,N-dimethylamino)-3-methoxyphenyl]phenyl]benzenesulfonamide;

- 4-[2-[4-(N,N-dimethylamino)-3-fluorophenyl]phenyl]benzenesulfonamide;  
4-[2-[3-chloro-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
5 4-[2-[4-(N,N-dimethylamino)-3-trifluoromethylphenyl]phenyl]benzenesulfonamide;  
4-[2-[3,4-di(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-(3,5-dimethylphenyl)phenyl]benzenesulfonamide;  
10 4-[2-(3,5-dimethoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-difluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dichlorophenyl)phenyl]benzenesulfonamide;  
4-[2-[3,5-di(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
15 4-[2-[3,5-di(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-(3,4,5-trimethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dimethoxy-4-methylphenyl)phenyl]benzenesulfonamide;  
20 4-[2-(3,5-difluoro-4-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dichloro-4-methylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3,5-di(trifluoromethyl)-4-methylphenyl]phenyl]benzenesulfonamide;  
25 4-[2-[3,5-di(N,N-dimethylamino)-4-methylphenyl]phenyl]benzenesulfonamide;  
4-[2-(3,5-dimethyl-4-methoxyphenyl)phenyl]benzenesulfonamide;  
30 4-[2-(3,4,5-trimethoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-difluoro-4-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dichloro-4-methoxyphenyl)phenyl]benzenesulfonamide;  
35 4-[2-[3,5-di(trifluoromethyl)-4-methoxyphenyl]phenyl]benzenesulfonamide;

- 4-[2-[3,5-di(N,N-dimethylamino)-4-methoxyphenyl]phenyl]benzenesulfonamide;  
4-[2-(3,5-dimethyl-4-fluorophenyl)phenyl]benzenesulfonamide;  
5 4-[2-(3,5-dimethoxy-4-fluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3,4,5-trifluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dichloro-4-fluorophenyl)phenyl]benzenesulfonamide;  
10 4-[2-[3,5-di(trifluoromethyl)-4-fluorophenyl]phenyl]benzenesulfonamide;  
4-[2-[3,5-di(N,N-dimethylamino)-4-fluorophenyl]phenyl]benzenesulfonamide;  
4-[2-(4-chloro-3,5-dimethylphenyl)phenyl]benzenesulfonamide;  
15 4-[2-(4-chloro-3,5-dimethoxyphenyl)phenyl]benzenesulfonamide;  
4-[2-(4-chloro-3,5-difluorophenyl)phenyl]benzenesulfonamide;  
20 4-[2-(3,4,5-trichlorophenyl)phenyl]benzenesulfonamide;  
4-[2-[4-chloro-3,5-di(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
4-[2-[4-chloro-3,5-di(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
25 4-[2-(3,5-dimethyl-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dimethoxy-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-difluoro-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
30 4-[2-(3,5-dichloro-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-[3,4,5-tri(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
35 4-[2-[3,5-di(N,N-dimethylamino)-4-trifluoromethylphenyl]phenyl]benzenesulfonamide;

- 4-[2-[3,5-dimethyl-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-[3,5-dimethoxy-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
5 4-[2-[3,5-difluoro-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-[3,5-dichloro-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-[4-(N,N-dimethylamino)-3,5-di(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
10 4-[2-[3,4,5-tri(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-(6-phenyl-1,3-benzodioxol-5-yl)benzenesulfonamide;  
4-[6-(3-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
15 4-[6-(3-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3-chlorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
20 4-[6-(3-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-[3-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;  
25 4-[6-(4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,4-dimethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
30 4-[6-(3-fluoro-4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3-chloro-4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3-methoxy-4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
35 4-[6-(4-methyl-3-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;



- 4-[6-[3-(N,N-dimethylamino)-4-methylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 5 4-[6-(4-methoxy-3-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3-fluoro-4-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3-chloro-4-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 10 4-[6-(3,4-dimethoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-methoxy-3-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 15 4-[6-[3-(N,N-dimethylamino)-4-methoxyphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-fluoro-3-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 20 4-[6-(3,4-difluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3-chloro-4-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 25 4-[6-(4-fluoro-3-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-fluoro-3-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3-(N,N-dimethylamino)-4-fluorophenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 30 4-[6-(4-chlorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-chloro-3-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 35 4-[6-(4-chloro-3-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;

- 4-[6-(3,4-dichlorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-chloro-3-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 5 4-[6-(4-chloro-3-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-chloro-3-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 10 4-[6-(3-methyl-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3-fluoro-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 15 4-[6-(3-chloro-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3-methoxy-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3,4-di(trifluoromethyl)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 20 4-[6-[3-(N,N-dimethylamino)-4-trifluoromethylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 25 4-[6-[4-(N,N-dimethylamino)-3-methylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-(N,N-dimethylamino)-3-fluorophenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3-chloro-4-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 30 4-[6-[4-(N,N-dimethylamino)-3-methoxyphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-(N,N-dimethylamino)-3-trifluoromethylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 35 4-[6-[3,4-di(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;

- 4-[6-(3,5-dimethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,5-difluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
5 4-[6-(3,5-dichlorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,5-dimethoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-[3,5-di(trifluoromethyl)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;  
10 4-[6-[3,5-di(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,4,5-trimethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
15 4-[6-(3,5-difluoro-4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,5-dichloro-4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,5-dimethoxy-4-methylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
20 4-[6-[3,5-di(trifluoromethyl)-4-methylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-[3,5-di(N,N-dimethylamino)-4-methylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;  
25 4-[6-(3,5-dimethyl-4-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,5-difluoro-4-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-(3,5-dichloro-4-methoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
30 4-[6-(3,4,5-trimethoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;  
4-[6-[3,5-di(trifluoromethyl)-4-methoxyphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;  
35 4-[6-[3,5-di(N,N-dimethylamino)-4-methoxyphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;

- 4-[6-(3,4,5-trimethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3,5-difluoro-4-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 5 4-[6-(3,5-dichloro-4-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3,5-dimethoxy-4-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 10 4-[6-[3,5-di(trifluoromethyl)-4-fluorophenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3,5-di(N,N-dimethylamino)-4-fluorophenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-chloro-3,5-dimethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 15 4-[6-(4-chloro-3,5-difluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3,4,5-trichlorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(4-chloro-3,5-dimethoxyphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 20 4-[6-[4-chloro-3,5-di(trifluoromethyl)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-chloro-3,5-di(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 25 4-[6-(3,5-dimethyl-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3,5-difluoro-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-(3,5-dichloro-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 30 4-[6-(3,5-dimethoxy-4-trifluoromethylphenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3,4,5-tri(trifluoromethyl)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 35 4-[6-[3,5-di(N,N-dimethylamino)-4-trifluoromethylphenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;

- 4-[6-[3,5-dimethyl-4-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-(N,N-dimethylamino)-3,5-difluorophenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 5 4-[6-[3,5-dichloro-4-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3,5-dimethoxy-4-(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[4-(N,N-dimethylamino)-3,5-
- 10 di(trifluoromethyl)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-[6-[3,4,5-tri(N,N-dimethylamino)phenyl]-1,3-benzodioxol-5-yl]benzenesulfonamide;
- 4-(4,5-difluoro-2-biphenyl)benzenesulfonamide;
- 15 4-[4,5-difluoro-2-(3-methylphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3-fluorophenyl)phenyl]benzenesulfonamide;
- 4-[2-(3-chlorophenyl)-4,5-
- 20 difluorophenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3-methoxyphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3-trifluoromethylphenyl)phenyl]benzenesulfonamide;
- 25 4-[4,5-difluoro-2-[3-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(4-methylphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,4-
- 30 dimethylphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3-fluoro-4-methylphenyl)phenyl]benzenesulfonamide;
- 4-[2-(3-chloro-4-methylphenyl)-4,5-
- difluorophenyl]benzenesulfonamide;
- 35 4-[4,5-difluoro-2-(3-methoxy-4-methylphenyl)phenyl]benzenesulfonamide;

- 4-[4,5-difluoro-2-(4-methyl-3-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[3-(N,N-dimethylamino)-4-methylphenyl]phenyl]benzenesulfonamide;  
5 4-[4,5-difluoro-2-(4-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(4-methoxy-3-methylphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide;  
10 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,4-dimethoxyphenyl)phenyl]benzenesulfonamide;  
15 4-[4,5-difluoro-2-(4-methoxy-3-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[3-(N,N-dimethylamino)-4-methoxyphenyl]phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(4-fluorophenyl)phenyl]benzenesulfonamide;  
20 4-[4,5-difluoro-2-(4-fluoro-3-methylphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,4-difluorophenyl)phenyl]benzenesulfonamide;  
25 4-[4,5-difluoro-2-(3-chloro-4-fluorophenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(4-fluoro-3-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(4-fluoro-3-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
30 4-[4,5-difluoro-2-[3-(N,N-dimethylamino)-4-fluorophenyl]phenyl]benzenesulfonamide;  
4-[2-(4-chlorophenyl)-4,5-difluorophenyl]benzenesulfonamide;  
35 4-[2-(4-chloro-3-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide;

- 4-[2-(4-chloro-3-fluorophenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[2-(3,4-dichlorophenyl)-4,5-difluorophenyl]benzenesulfonamide;  
5 4-[2-(4-chloro-3-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[2-(4-chloro-3-trifluoromethylphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[2-[4-chloro-3-(N,N-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide;  
10 4-[4,5-difluoro-2-(4-(trifluoromethyl)phenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3-methyl-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
15 4-[4,5-difluoro-2-(3-fluoro-4-trifluoromethylphenyl)phenyl]benzenesulfonamide;  
4-[2-(3-chloro-4-trifluoromethylphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3-methoxy-4-(trifluoromethyl)phenyl)phenyl]benzenesulfonamide;  
20 4-[4,5-difluoro-2-[3,4-di(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[3-(N,N-dimethylamino)-4-trifluoromethylphenyl]phenyl]benzenesulfonamide;  
25 4-[4,5-difluoro-2-[4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[4-(N,N-dimethylamino)-3-methylphenyl]phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[4-(N,N-dimethylamino)-3-fluorophenyl]phenyl]benzenesulfonamide;  
30 4-[2-[3-chloro-4-(N,N-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[4-(N,N-dimethylamino)-3-methoxyphenyl]phenyl]benzenesulfonamide;  
35 4-[4,5-difluoro-2-[4-(N,N-dimethylamino)-3-(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;

- 4-[4,5-difluoro-2-[3,4-di(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,5-dimethylphenyl)phenyl]benzenesulfonamide;
- 5 4-[4,5-difluoro-2-(3,5-difluorophenyl)phenyl]benzenesulfonamide;
- 4-[2-(3,5-dichlorophenyl)-4,5-difluorophenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,5-dimethoxyphenyl)phenyl]benzenesulfonamide;
- 10 4-[4,5-difluoro-2-[3,5-di(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-[3,5-di(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;
- 15 4-[4,5-difluoro-2-(3,4,5-trimethylphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,5-difluoro-4-methylphenyl)phenyl]benzenesulfonamide;
- 4-[2-(3,5-dichloro-4-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- 20 4-[4,5-difluoro-2-(3,5-dimethoxy-4-methylphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-[3,5-di(trifluoromethyl)-4-methylphenyl]phenyl]benzenesulfonamide;
- 25 4-[4,5-difluoro-2-[3,5-di(N,N-dimethylamino)-4-methylphenyl]phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,5-dimethyl-4-methoxyphenyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,5-difluoro-4-methoxyphenyl)phenyl]benzenesulfonamide;
- 30 4-[2-(3,5-dichloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3,4,5-trimethoxyphenyl)phenyl]benzenesulfonamide;
- 35 4-[4,5-difluoro-2-[3,5-di(trifluoromethyl)-4-methoxyphenyl]phenyl]benzenesulfonamide;



- 4-[4,5-difluoro-2-(3,5-di(N,N-dimethylamino)-4-methoxyphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,5-dimethyl-4-fluorophenyl)phenyl]benzenesulfonamide;  
5 4-[4,5-difluoro-2-(3,4,5-difluorophenyl)phenyl]benzenesulfonamide;  
4-[2-(3,5-dichloro-4-fluorophenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,5-dimethoxy-4-fluorophenyl)phenyl]benzenesulfonamide;  
10 4-[4,5-difluoro-2-(3,5-di(trifluoromethyl)-4-fluorophenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,5-di(N,N-dimethylamino)-4-fluorophenyl)phenyl]benzenesulfonamide;  
15 4-[2-(4-chloro-3,5-dimethylphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[2-(4-chloro-3,5-difluorophenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,4,5-trichlorophenyl)phenyl]benzenesulfonamide;  
20 4-[2-(4-chloro-3,5-dimethoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[2-[4-chloro-3,5-di(trifluoromethyl)phenyl]-4,5-difluorophenyl]benzenesulfonamide;  
25 4-[2-[4-chloro-3,5-di(N,N-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,5-dimethyl-4-(trifluoromethyl)phenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,5-difluoro-4-(trifluoromethyl)phenyl)phenyl]benzenesulfonamide;  
30 4-[2-(3,5-dichloro-4-(trifluoromethyl)phenyl)-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-(3,5-dimethoxy-4-(trifluoromethyl)phenyl)phenyl]benzenesulfonamide;  
35 4-[4,5-difluoro-2-(3,4,5-tri(trifluoromethyl)-phenyl)phenyl]benzenesulfonamide;

- 4-[4,5-difluoro-2-[3,5-di(N,N-dimethylamino)-4-(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[3,5-dimethyl-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
5 4-[4,5-difluoro-2-[3,5-difluoro-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[2-[3,5-dichloro-4-(N,N-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[3,5-dimethoxy-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
10 4-[4,5-difluoro-2-[3,5-di(trifluoromethyl)-4-(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[3,4,5-tri(N,N-dimethylamino)phenyl]phenyl]benzenesulfonamide;  
15 4-(3,4,5,6-tetrafluoro-2-biphenyl)benzenesulfonamide;  
4-[2-(3-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
20 4-[2-(3-chlorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[3,4,5,6-tetrafluoro-2-(3-(trifluoromethyl)phenyl)phenyl]benzenesulfonamide;  
25 4-[2-[3-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
30 4-[2-(3,4-dimethylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-fluoro-4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-chloro-4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
35 4-[2-(3-methoxy-4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;

- 4-[2-(4-methyl-3-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[3-(N,N-dimethylamino)-4-methylphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
5 4-[2-(4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-methyl-4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-fluoro-4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
10 4-[2-(3-chloro-4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3,4-dimethoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
15 4-[2-(4-methoxy-3-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[3-(N,N-dimethylamino)-4-methoxyphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(4-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
20 4-[2-(4-fluoro-3-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3,4-difluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
25 4-[2-(3-chloro-4-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(4-fluoro-3-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(4-fluoro-3-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
30 4-[2-[3-(N,N-dimethylamino)-4-fluorophenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(4-chlorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
35 4-[2-(4-chloro-3-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;

- 4-[2-(4-chloro-3-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3,4-dichlorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
5 4-[2-(4-chloro-3-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(4-chloro-3-trifluoromethylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[4-chloro-3-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
10 4-[3,4,5,6-tetrafluoro-2-[4-(trifluoromethyl)phenyl]phenyl]benzenesulfonamide;  
4-[2-(3-methyl-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
15 4-[2-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-chloro-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-(3-methoxy-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
20 4-[2-[3,4-di(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[3-(N,N-dimethylamino)-4-(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
25 4-[2-[4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[4-(N,N-dimethylamino)-3-methylphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[4-(N,N-dimethylamino)-3-fluorophenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
30 4-[2-[3-chloro-4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
4-[2-[4-(N,N-dimethylamino)-3-methoxyphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;  
35 4-[2-[4-(N,N-dimethylamino)-3-(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;

- 4-[2-[3,4-di(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dimethylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 5 4-[2-(3,5-difluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dichlorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 10 4-[2-(3,5-dimethoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-di(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-di(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 15 4-[2-(3,4,5-trimethylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-difluoro-4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dichloro-4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 20 4-[2-(3,5-dimethoxy-4-methylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-di(trifluoromethyl)-4-methylphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 25 4-[2-[3,5-di(N,N-dimethylamino)-4-methylphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dimethyl-4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-difluoro-4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 30 4-[2-(3,5-dichloro-4-methoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,4,5-trimethoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 35 4-[2-[3,5-di(trifluoromethyl)-4-methoxyphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;

- 4-[2-[3,5-di(N,N-dimethylamino)-4-methoxyphenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dimethyl-4-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 5 4-[2-(3,4,5-trifluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dichloro-4-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dimethoxy-4-fluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 10 4-[2-[3,5-di(trifluoromethyl)-4-fluorophenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-di(N,N-dimethylamino)-4-fluorophenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 15 4-[2-(4-chloro-3,5-dimethylphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(4-chloro-3,5-difluorophenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[3,4,5,6-tetrafluoro-2-(3,4,5-trichlorophenyl)phenyl]benzenesulfonamide;
- 20 4-[2-(4-chloro-3,5-dimethoxyphenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[4-chloro-3,5-di(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 25 4-[2-[4-chloro-3,5-di(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dimethyl-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-difluoro-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 30 4-[2-(3,5-dichloro-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(3,5-dimethoxy-4-(trifluoromethyl)phenyl)-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 35 4-[2-[3,4,5-tri(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;

- 4-[2-[3,5-di(N,N-dimethylamino)-4-(trifluoromethyl)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-dimethyl-4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 5 4-[2-[3,5-difluoro-4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-dichloro-4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 10 4-[2-[3,5-dimethoxy-4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-[3,5-di(trifluoromethyl)-4-(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 15 4-[2-[3,4,5-tri(N,N-dimethylamino)phenyl]-3,4,5,6-tetrafluorophenyl]benzenesulfonamide;
- 4-[2-(4-hydroxymethylphenyl)phenyl]benzenesulfonamide;
- 4-[2-(4-methylthiophenyl)phenyl]benzenesulfonamide;
- 4-[2-(4-cyanophenyl)phenyl]benzenesulfonamide;
- 20 4-[2-(4-aminophenyl)phenyl]benzenesulfonamide;
- 4-[2-(4-hydroxyphenyl)phenyl]benzenesulfonamide;
- 4-[2-[4-(N-methylamino)phenyl]phenyl]benzenesulfonamide;
- 4-[2-(4-methoxymethylphenyl)phenyl]benzenesulfonamide;
- 4-[2-(1,3-benzodioxol-5-yl)-4,5-difluorophenyl]benzenesulfonamide;
- 25 4-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,5-difluorophenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(5-methylpyridin-2-yl)phenyl]benzenesulfonamide;
- 30 4-[4,5-difluoro-2-(6-methylpyridin-3-yl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(2-thienyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(3-furyl)phenyl]benzenesulfonamide;
- 4-[4,5-difluoro-2-(4-hydroxymethylphenyl)phenyl]benzenesulfonamide;
- 35 4-[4,5-difluoro-2-(4-methylthiophenyl)phenyl]benzenesulfonamide;

- 4-[2-(4-cyanophenyl)-4,5-difluoro-phenyl]benzenesulfonamide;  
4-[2-(4-aminophenyl)-4,5-difluoro-phenyl]benzenesulfonamide;  
5 4-[4,5-difluoro-2-(4-hydroxyphenyl)phenyl]benzenesulfonamide;  
4-[4,5-difluoro-2-[4-(N-methylamino)phenyl]phenyl]benzenesulfonamide; and  
4-[4,5-difluoro-2-(4-methoxymethylphenyl)phenyl]benzenesulfonamide.  
10

A second family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 15 2-[4-(methylsulfonyl)phenyl]-1-phenylbenzene;  
1-(3-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
20 1-(3-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4-dimethylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3-methoxy-4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
25 1-(3-fluoro-4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3-chloro-4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
30 1-(4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3-methyl-4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4-dimethoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
35 2-fluoro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene;



- 2-chloro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene;  
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(4-fluoro-3-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
5 1-(4-fluoro-3-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
10 2-chloro-1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene;  
1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(4-chloro-3-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
15 1-(4-chloro-3-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(4-chloro-3-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4-dichlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
20 1-(3,5-dimethylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,5-dimethoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
25 1-(3,5-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,5-dichlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4,5-trimethylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
30 1-(3,5-dimethoxy-4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,5-difluoro-4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
35 1-(3,5-dichloro-4-methylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

- 1-(3,5-dimethyl-4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4,5-trimethoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
5 1-(3,5-difluoro-4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,5-dichloro-4-methoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,5-dimethyl-4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
10 1-(3,5-dimethoxy-4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4,5-trifluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
15 1-(3,5-dichloro-4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(4-chloro-3,5-dimethylphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(4-chloro-3,5-dimethoxyphenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
20 1-(4-chloro-3,5-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
1-(3,4,5-trichlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;  
25 6-[4-(methylsulfonyl)phenyl]-5-phenyl-1,3-benzodioxole;  
5-(3-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;  
5-(3-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;  
30 5-(3-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;  
5-(3-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;  
5-(4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;  
35 5-(3,4-dimethylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;

- 5-(3-fluoro-4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3-chloro-4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5 5-(3-methoxy-4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3-methyl-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 10 5-(3-fluoro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 15 5-(3,4-dimethoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(4-fluoro-3-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 20 5-(3,4-difluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 25 5-(4-fluoro-3-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(4-chlorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(4-chloro-3-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 30 5-(4-chloro-3-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,4-dichlorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 35 5-(4-chloro-3-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;

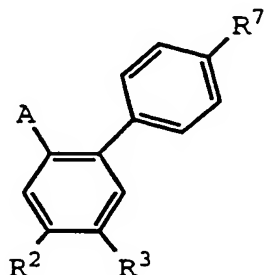
- 5-(3,5-dimethylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-difluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5 5-(3,5-dichlorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-dimethoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 10 5-(3,4,5-trimethylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-difluoro-4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-dichloro-4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 15 5-(3,5-dimethoxy-4-methylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-dimethyl-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 20 5-(3,5-difluoro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,4,5-trimethoxyphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 25 5-(3,5-dimethyl-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,4,5-trifluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(3,5-dichloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 30 5-(3,5-dimethoxy-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5-(4-chloro-3,5-dimethylphenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 35 5-(4-chloro-3,5-difluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole;

- 5-(3,4,5-trichlorophenyl)-6-[4-(methylsulfonyl)phenyl]-  
1,3-benzodioxole;
- 5-(4-chloro-3,5-dimethoxyphenyl)-6-[4-  
(methylsulfonyl)phenyl]-1,3-benzodioxole;
- 5 1,2-difluoro-5-[4-(methylsulfonyl)phenyl]-4-  
phenylbenzene;
- 1,2-difluoro-4-(3-methylphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3-fluorophenyl)-5-[4-  
10 (methylsulfonyl)phenyl]benzene;
- 4-(3-chlorophenyl)-1,2-difluoro-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3-methoxyphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 15 1,2-difluoro-4-(4-methylphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3,4-dimethylphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3-fluoro-4-methylphenyl)-5-[4-  
20 (methylsulfonyl)phenyl]benzene;
- 4-(3-chloro-4-methylphenyl)-1,2-difluoro-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3-methoxy-4-methylphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 25 1,2-difluoro-4-(4-methoxyphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(4-methoxy-3-methylphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3-fluoro-4-methoxyphenyl)-5-[4-  
30 (methylsulfonyl)phenyl]benzene;
- 4-(3-chloro-4-methoxyphenyl)-1,2-difluoro-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 1,2-difluoro-4-(3,4-dimethoxyphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;
- 35 1,2-difluoro-4-(4-fluorophenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene;

- 1,2-difluoro-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
1,2-difluoro-4-(3,4-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
5 4-(3-chloro-4-fluorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
1,2-difluoro-4-(4-fluoro-3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
4-(4-chlorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
10 4-(4-chloro-3-methylphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
4-(4-chloro-3-fluorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
15 4-(3,4-dichlorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
4-(4-chloro-3-methoxyphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
1,2-difluoro-4-(3,5-dimethylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
20 1,2-difluoro-4-(3,5-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
4-(3,5-dichlorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
25 1,2-difluoro-4-(3,5-dimethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
1,2-difluoro-4-(3,4,5-trimethylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
1,2-difluoro-4-(3,5-difluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
30 4-(3,5-dichloro-4-methylphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
1,2-difluoro-4-(3,5-dimethoxy-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
35 1,2-difluoro-4-(3,5-dimethyl-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;

- 1,2-difluoro-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
 4-(3,5-dichloro-4-methoxyphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
 5 1,2-difluoro-4-(3,4,5-trimethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
 4-(3,5-dimethyl-4-fluorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
 1,2-difluoro-4-(3,4,5-trifluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
 10 4-(3,5-dichloro-4-fluorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
 1,2-difluoro-4-(3,5-dimethoxy-4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
 15 4-(4-chloro-3,5-dimethylphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
 4-(4-chloro-3,5-difluorophenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
 1,2-difluoro-4-(3,4,5-trichlorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
 20 4-(4-chloro-3,5-dimethoxyphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene;  
 5-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-1,3-benzodioxole;  
 25 2-chloro-4-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-N,N-dimethylbenzenamine;  
 6-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1,4-benzodioxin;  
 30 1,2-dichloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene;  
 2-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-5-methylpyridine;  
 5-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-2-methylpyridine; and  
 35 1,2-difluoro-5-[4-(methylsulfonyl)phenyl]-4-(2-thiazolyl)benzene.

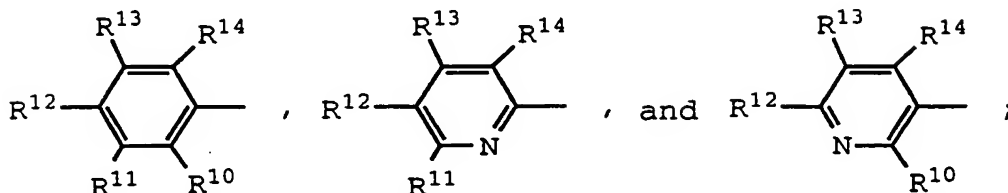
Within Formula I there is a subclass of compounds of high interest represented by Formula II:



**II**

5

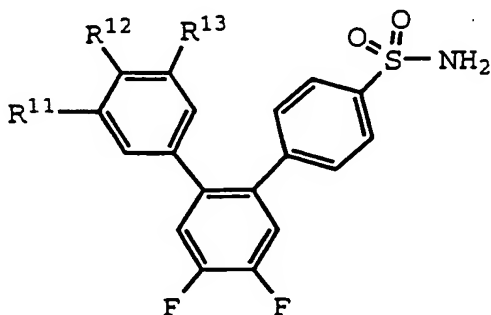
wherein A is selected from



- 10 wherein each of  $R^2$  and  $R^3$  is independently selected from hydrido and halo; or wherein  $R^2$  and  $R^3$  together form  $-OCH_2O-$ ; wherein each of  $R^{10}$  through  $R^{14}$  is independently selected from hydrido, lower alkyl, halo, lower alkoxy, lower haloalkyl, and lower
- 15 dialkylamino; or wherein  $R^{11}$  and  $R^{12}$  together form  $-O(CH_2)_nO-$ ; wherein  $n$  is 1-2, inclusive; and wherein  $R^7$  is selected from lower alkylsulfonyl and aminosulfonyl; or a pharmaceutically-acceptable salt thereof.

20

Within Formula I there is a second subclass of compounds of high interest represented by Formula III:

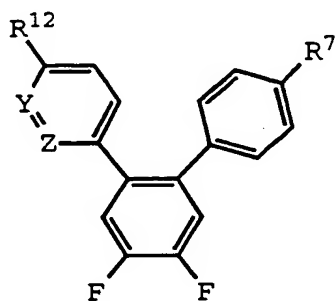


**III**



wherein each of  $R^{11}$  through  $R^{13}$  is independently selected from hydrido, halo, lower alkoxy, lower haloalkyl, amino, lower alkylamino, lower dialkylamino, and lower haloalkoxy; or wherein  $R^{11}$  and  $R^{12}$  together form  $-O(CH_2)_nO-$ ; wherein  $n$  is 1-2, inclusive; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a third subclass of compounds of high interest represented by Formula IV:



IV

wherein  $Y$  is  $CR^{11}$  or  $N$ ; wherein  $Z$  is  $CR^{10}$  or  $N$ ; wherein each of  $R^{10}$  through  $R^{12}$  is independently selected from hydrido and lower alkyl; wherein  $R^7$  is aminosulfonyl or methylsulfonyl; provided one of  $Y$  and  $Z$  is  $N$ ; or a pharmaceutically-acceptable salt thereof.

The term "hydrido" denotes a single hydrogen atom ( $H$ ). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ( $-CH_2-$ ) radical. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl,

n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalalkyl and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, tert-butoxy, methylenedioxy and ethylenedioxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl

radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" and "lower haloalkoxy" radicals. Examples of such radicals include trifluoromethoxy, chloromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3-nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of heteroaryl radicals include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-

1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, 5 isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered 10 heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, 15 isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered 20 heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur 25 atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the 30 like. Preferred heteroaryl radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, 35 benzodioxolyl, benzodioxanyl, pyridyl, thienyl, pyrazolyl, isoxazolyl, pyrrolyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. The term "sulfonyl", whether used

alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals  $-SO_2-$ .

"Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl" denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ( $-SO_2NH_2$ ). The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes  $-CO_2H$ . The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals forming N-alkylamino and N,N-dialkylamino radicals, respectively. Preferred alkylamino radicals are "lower alkylamino" having alkyl portions of one to six carbon atoms. Examples include N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The present invention comprises a pharmaceutical composition for the treatment of inflammation or an inflammation-associated disorder, such as arthritis, comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a therapeutic method of treating inflammation or an inflammation-associated disorder in a subject, the method comprising treating a subject having or susceptible to such

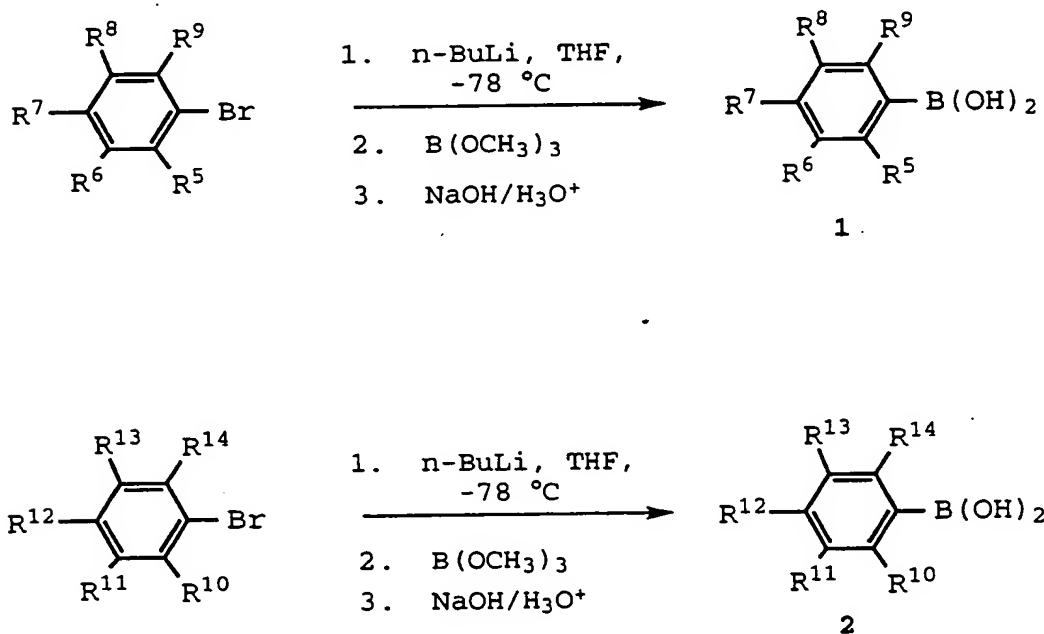
inflammation or inflammation-associated disorder with a therapeutically-effective amount of a compound of Formula I.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic,  $\beta$ -hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

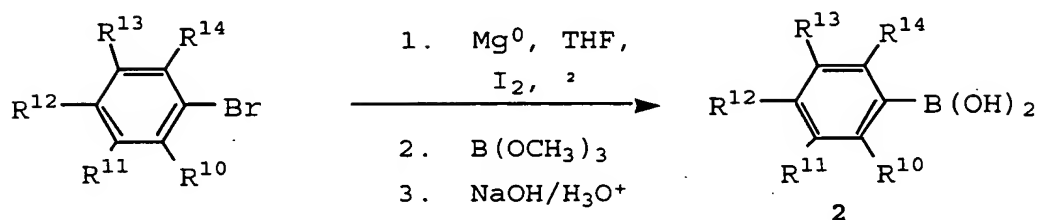
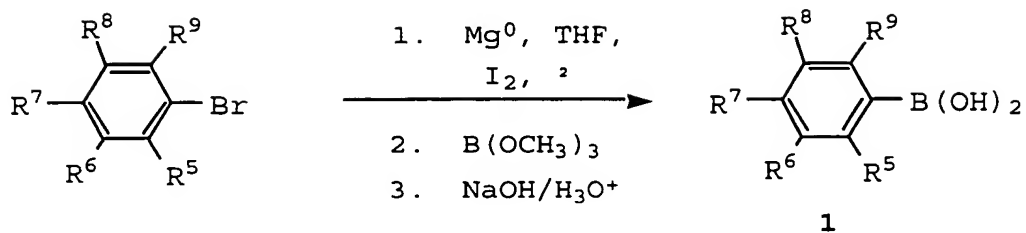
The compounds of the invention can be synthesized according to the following procedures of Schemes I-XIX, wherein the R<sup>1</sup>-R<sup>14</sup> substituents are as defined for Formulas I-IV, above, except where further noted. U.S. Patent Application Serial No. 08/346,433 is incorporated by reference.

## SCHEME I



Synthetic Scheme I shows the three step procedure for the preparation of the prerequisite substituted phenylboronic acids 1 and 2 from commercially available phenyl bromides. In step one, halogen-metal interchange in THF at  $-78\text{ }^{\circ}\text{C}$  generates the corresponding organolithium reagents. In step two, the organolithium species are reacted with trimethyl borate to give the corresponding methyl esters. In step three, hydrolysis with aqueous sodium hydroxide provides the substituted phenylboronic acids 1 and 2, respectively.

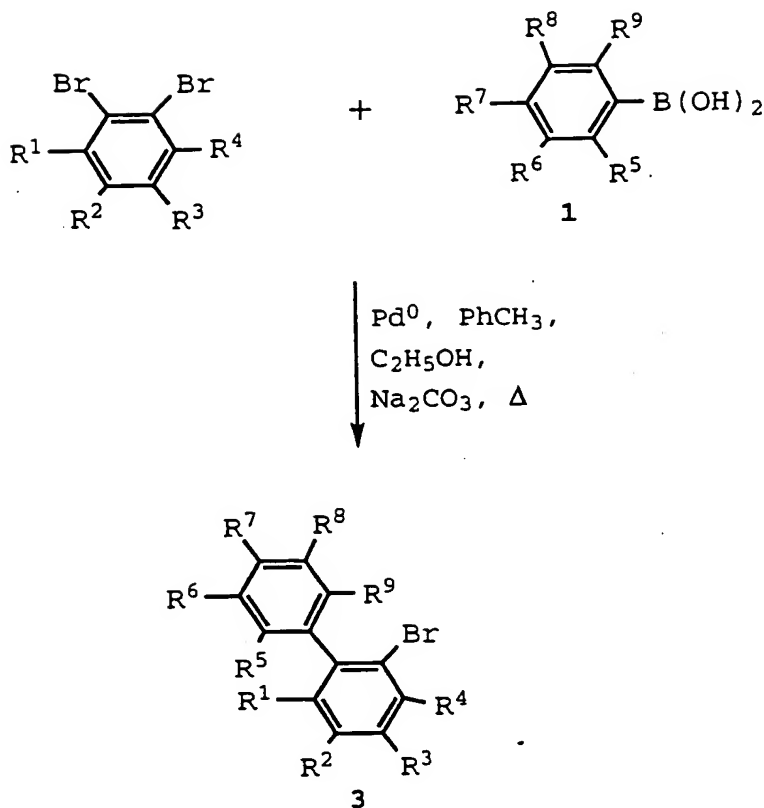
## SCHEME II



5        Synthetic Scheme II shows an alternative three  
 step procedure for the preparation of the prerequisite  
 substituted phenylboronic acids 1 and 2 from  
 commercially available phenyl bromides. In step one,  
 reaction with magnesium metal in THF at reflux in the  
 10      presence of an iodine catalyst generates the  
 corresponding Grignard reagents. In step two, the  
 Grignard reagents are reacted with trimethyl borate to  
 give the corresponding methyl esters. In step three,  
 hydrolysis with aqueous sodium hydroxide provides the  
 15      substituted phenylboronic acids 1 and 2, respectively.

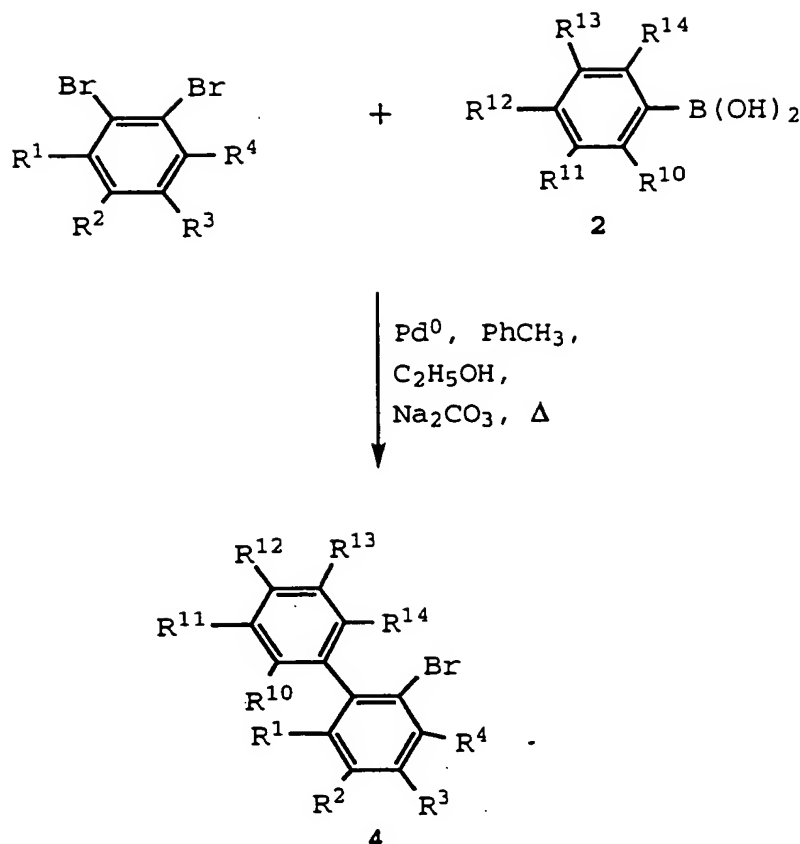


## SCHEME III



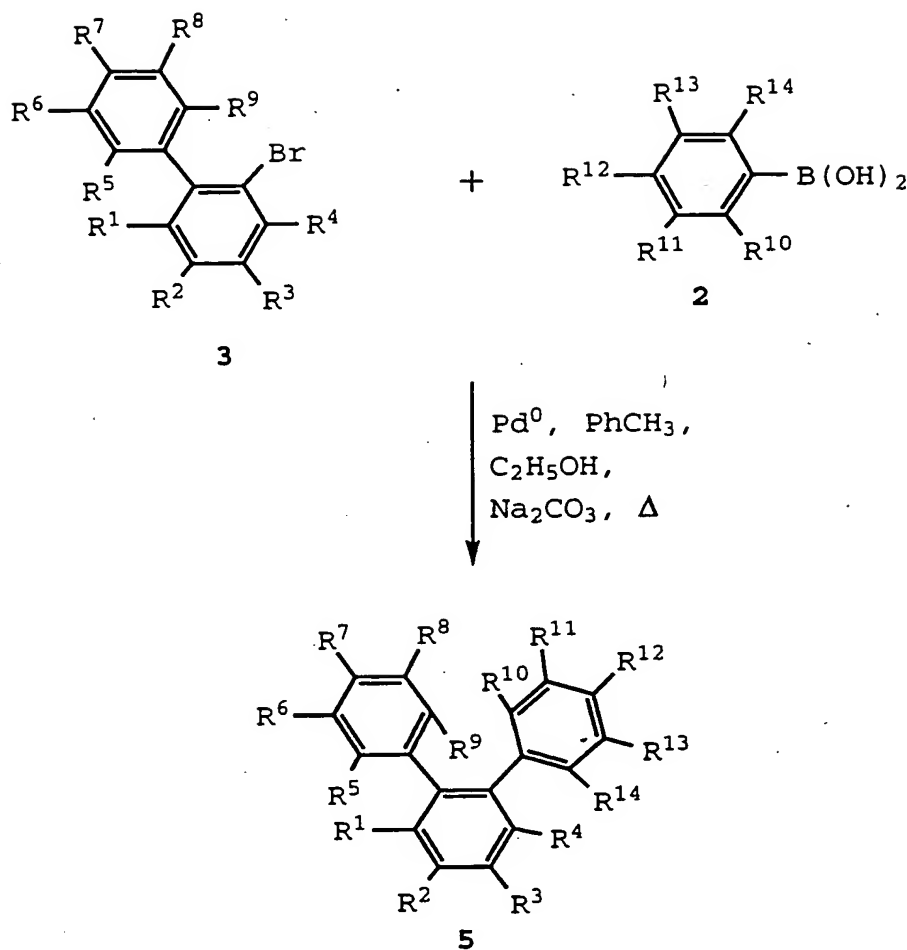
- 5 Synthetic Scheme III shows the procedure for the preparation of the substituted 2-bromo-biphenyl intermediates 3 from commercially available 1,2-dibromobenzenes and the appropriate substituted phenylboronic acid 1 (prepared in Synthetic Schemes I and II). Using a coupling procedure similar to the one developed by Suzuki et al. [Synth. Commun., 11, 513 (1981)], 1,2-dibromobenzenes are reacted with 1 in toluene/ethanol at reflux in the presence of a Pd<sup>0</sup> catalyst, e.g.,
- 10 tetakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding substituted 2-bromo-biphenyl intermediates 3.

## SCHEME IV



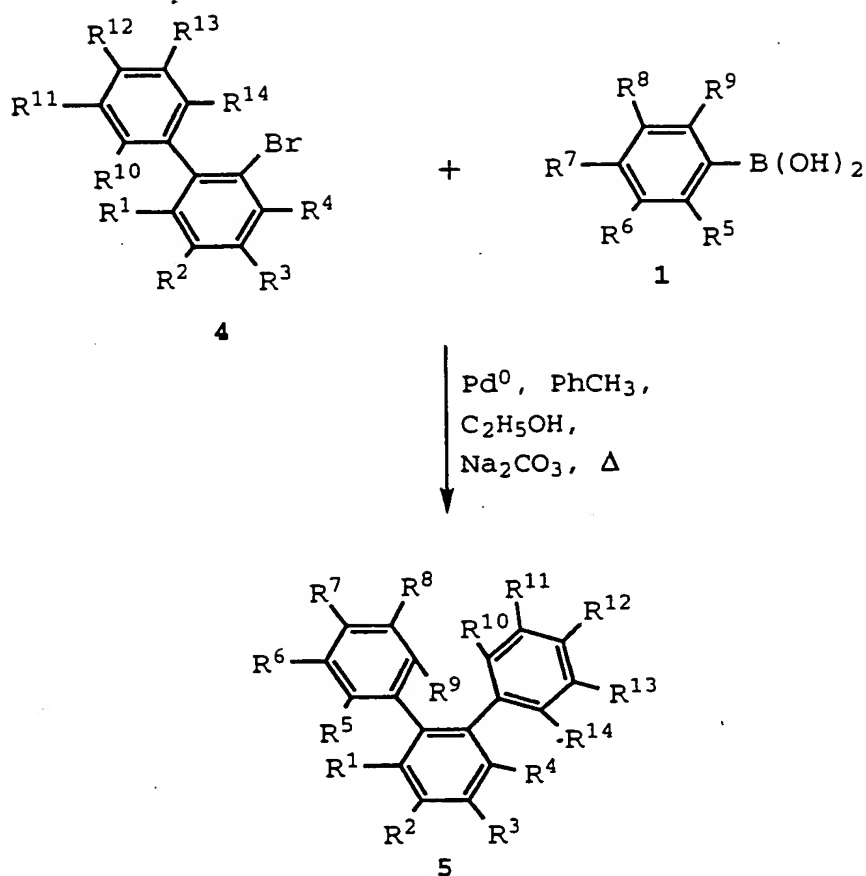
- 5        Synthetic Scheme IV shows the procedure for the preparation of the substituted 2-bromobiphenyl intermediates 4 from commercially available 1,2-dibromobenzenes and the appropriate substituted phenylboronic acids 2 (prepared in Synthetic Schemes I and II). Using a coupling procedure similar to the one developed by Suzuki et al. (Synthetic Scheme III), 1,2-dibromobenzenes are reacted with 2 in toluene/ethanol at reflux in the presence of a Pd<sup>0</sup> catalyst, e.g., tetrakis (triphenylphosphine)palladium(0), and 2M sodium
- 10
- 15        carbonate to give the corresponding substituted 2-bromobiphenyl intermediates 4.

## SCHEME V



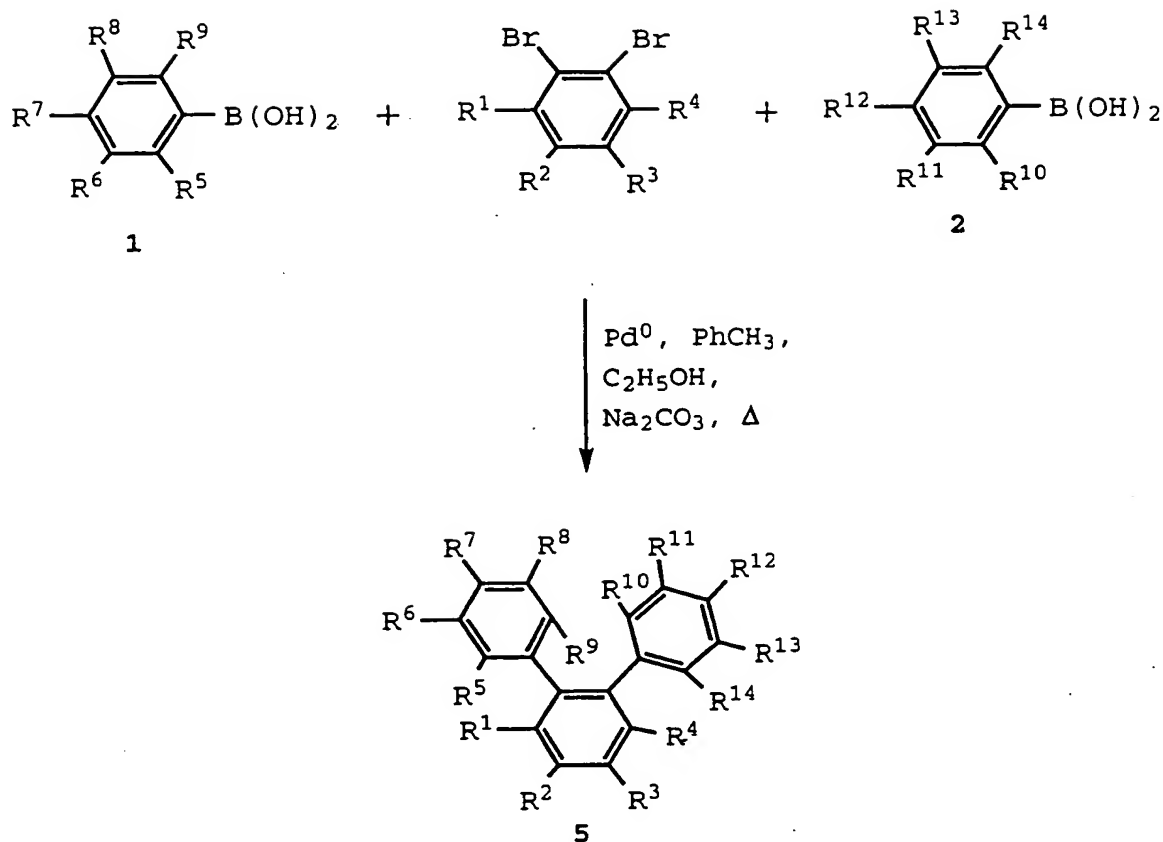
5 Synthetic Scheme V shows the procedure for the preparation of 1,2-diarylbenzene antiinflammatory agents 5 from 2-bromo-biphenyl intermediates 3 (prepared in Synthetic Scheme III) and the appropriate substituted phenylboronic acids 2 (prepared in Synthetic Schemes I and II). Using a coupling procedure similar to the one developed by Suzuki et al. (Synthetic Scheme III), intermediates 3 are reacted with 2 in toluene/ethanol at reflux in the presence of a Pd<sup>0</sup> catalyst, e.g., tetrakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents 5 of this invention.

## SCHEME VI



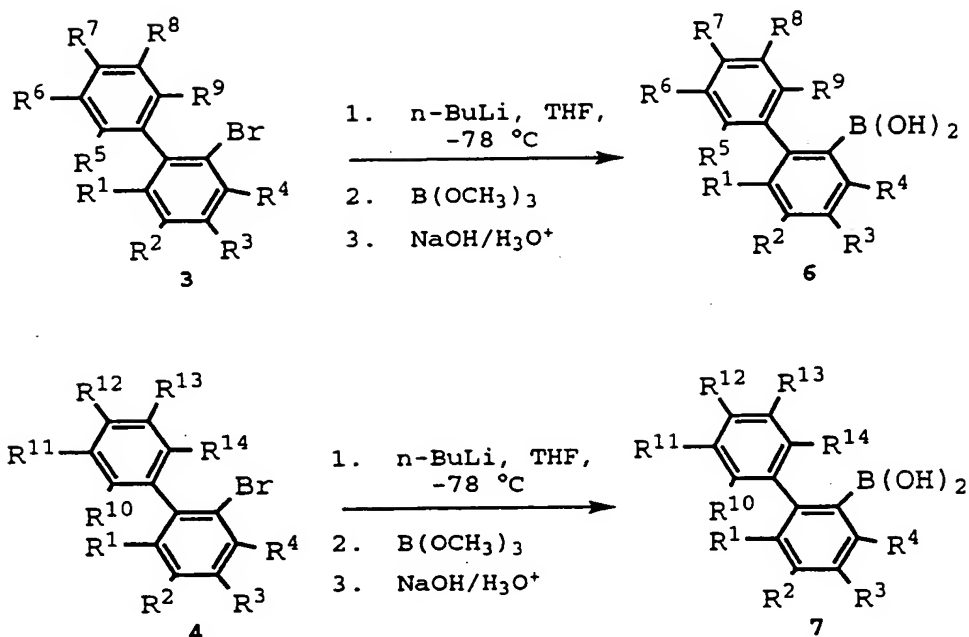
5 Synthetic Scheme VI shows the procedure for the preparation of 1,2-diarylbenzene antiinflammatory agents 5 from 2-bromo-biphenyl intermediates 4 (prepared in Synthetic Scheme IV) and the appropriate substituted phenylboronic acids 1 (prepared in Synthetic Schemes I and II). Using a coupling procedure similar to the one developed by Suzuki et al. (Synthetic Scheme III), intermediates 4 are reacted with 1 in toluene/ethanol at reflux in the presence of a Pd<sup>0</sup> catalyst, e.g., tetrakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents 5 of this invention.

## SCHEME VII



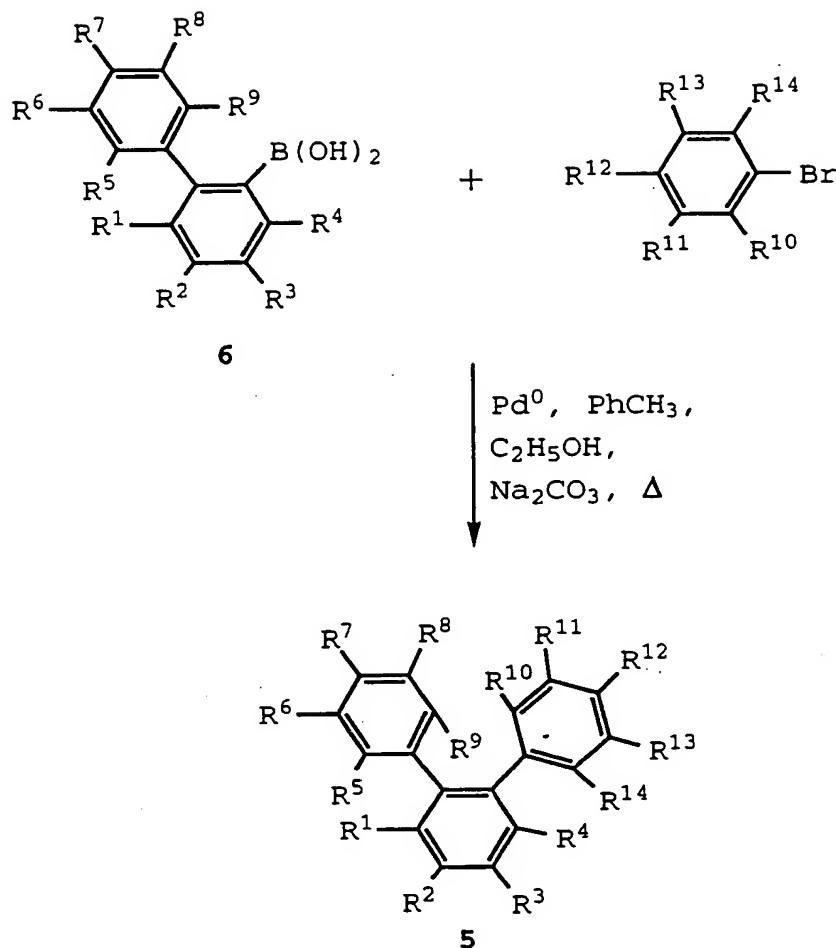
- 5 Synthetic Scheme VII shows an alternative one step procedure for the preparation of 1,2-diarylbenzene antiinflammatory agents 5 from commercially available 1,2-dibromobenzenes and the appropriate substituted phenylboronic acids 1 and 2 (prepared in Synthetic
- 10 Schemes I and II). Using a coupling procedure similar to the one developed by Suzuki *et al.* (Synthetic Scheme III), an equimolar mixture of 1,2-dibromobenzenes, 1 and 2 are reacted in toluene/ethanol at reflux in the presence of a  $Pd^0$  catalyst, e.g.,
- 15 tetrakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents 5 of this invention.

## SCHEME VIII



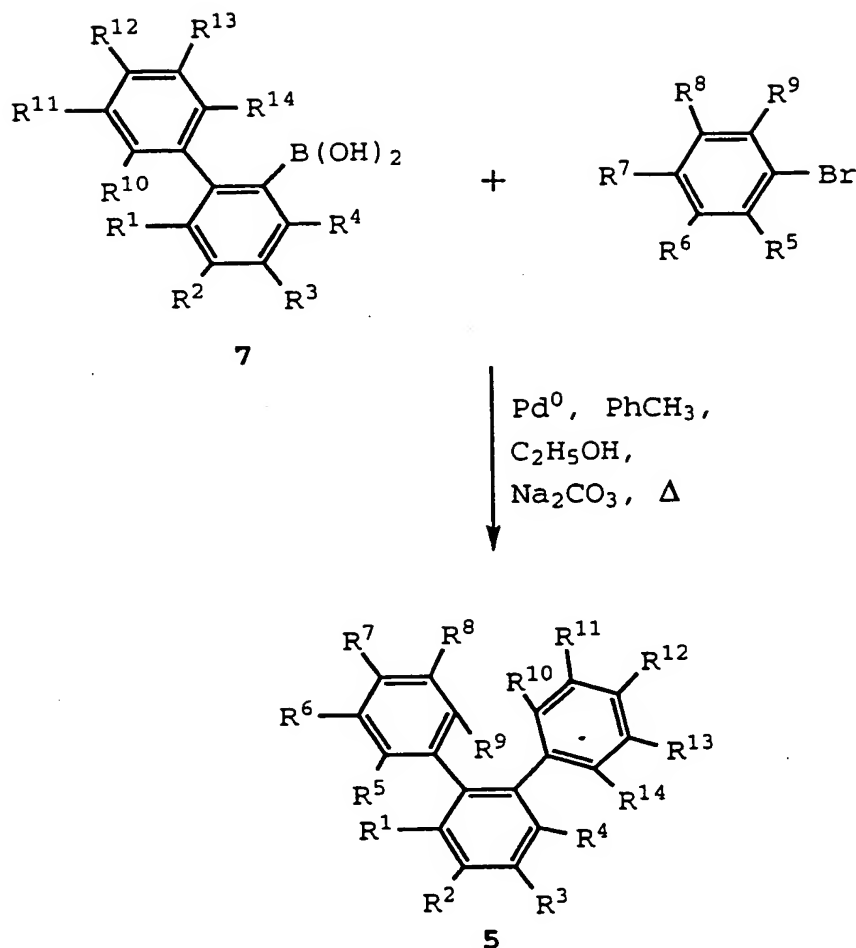
- 5 Synthetic Scheme VIII shows the three step procedure for the preparation of the 2-arylphenylboronic acids 6 and 7 from corresponding 2-bromobiphenyl intermediates 3 (prepared in Synthetic Scheme III) and 4 (prepared in Synthetic Scheme IV),
- 10 respectively. In step one, halogen-metal interchange in THF at  $-78^\circ\text{C}$  generates the corresponding organolithium reagents. In step two, the organolithium species are reacted with trimethyl borate to give the corresponding methyl esters. In step three, hydrolysis with aqueous
- 15 sodium hydroxide provides the substituted phenylboronic acids 6 and 7, respectively.

## SCHEME IX



- 5 Synthetic Scheme IX shows the procedure for the preparation of 1,2-diarylbenzene antiinflammatory agents 5 from commercially available substituted phenyl bromides and 2-aryl-phenylboronic acids 6 (prepared in Synthetic Scheme VIII). Using a coupling procedure
- 10 similar to the one developed by Suzuki et al. (Synthetic Scheme III), substituted phenyl bromides are reacted with 6 in toluene/ethanol at reflux in the presence of a  $Pd^0$  catalyst, e.g.,
- 15 tetrakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents 5 of this invention.

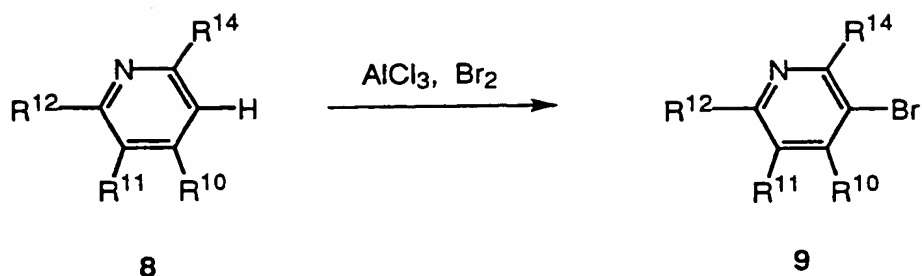
## SCHEME X



- 5 Synthetic Scheme X shows the procedure for the preparation of 1,2-diarylbenzene antiinflammatory agents 5 from commercially available substituted phenyl bromides and 2-aryl-phenylboronic acids 7 (prepared in Synthetic Scheme VIII). Using a coupling procedure
- 10 similar to the one developed by Suzuki et al. (Synthetic Scheme III), substituted phenyl bromides are reacted with 7 in toluene/ethanol at reflux in the presence of a Pd<sup>0</sup> catalyst, e.g., tetrakis(triphenylphosphine) palladium(0), and 2M sodium carbonate to give the
- 15 corresponding 1,2-diarylbenzene antiinflammatory agents 5 of this invention.

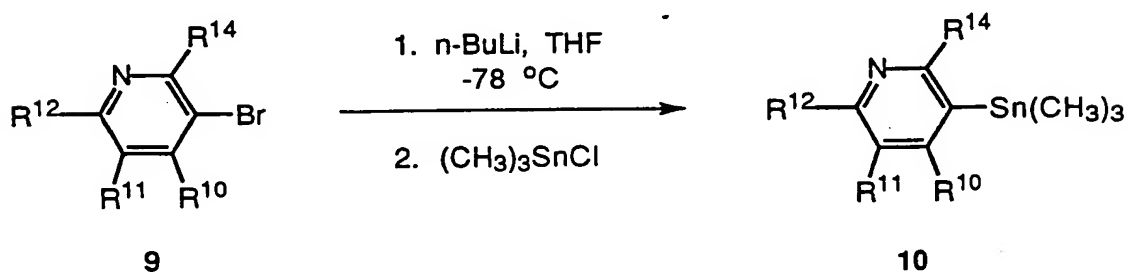


## SCHEME XI



5        Synthetic Scheme XI shows the procedure for the  
preparation of 3-bromopyridines 9 from commercially  
available pyridines 8. Using a procedure similar to the  
one developed by Reitz et al. [US Patent No. 5,155,177],  
pyridines 8 are reacted with bromine in the presence of  
10    aluminum chloride to give the 3-bromopyridines 9.

## SCHEME XII

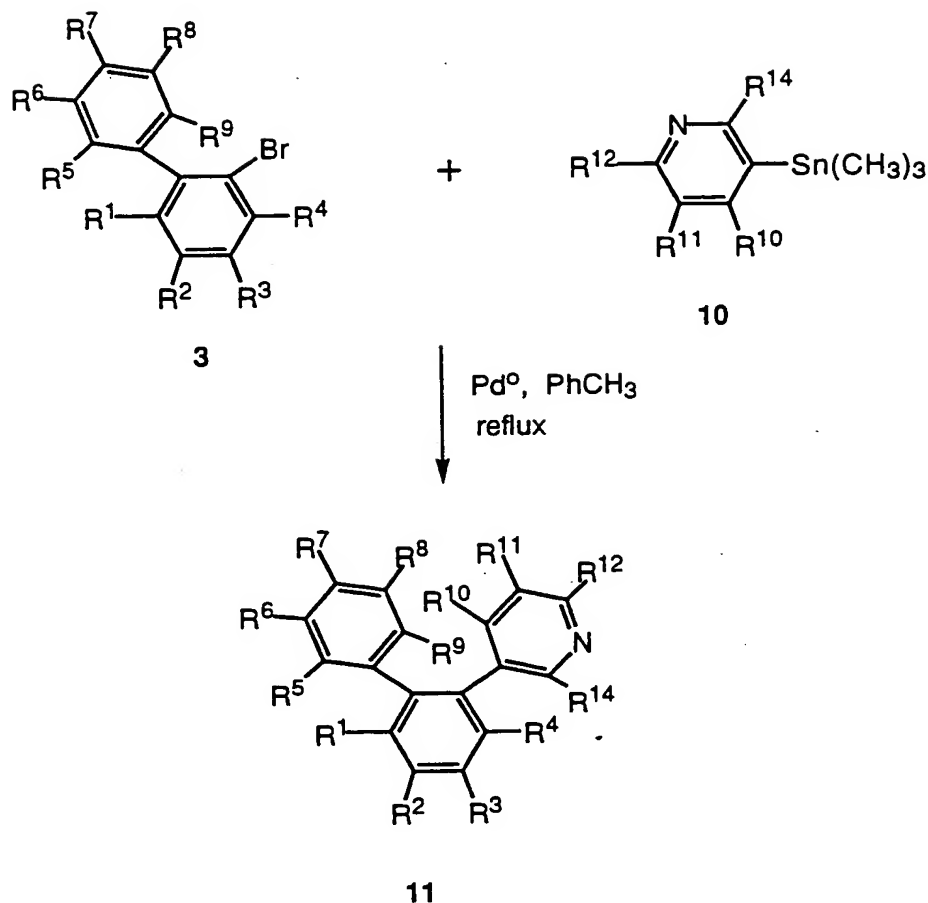


15

Synthetic Scheme XII shows the procedure for the  
preparation of pyridyltin intermediates 10 from 3-  
bromopyridines 9 (prepared in Synthetic Scheme XI). In  
step one, halogen-lithium interchange in THF at -78 °C  
generates the corresponding organolithium reagents. In  
20    step two, the organolithium species are reacted with  
trimethyltin chloride to give the corresponding  
pyridyltin intermediates 10.

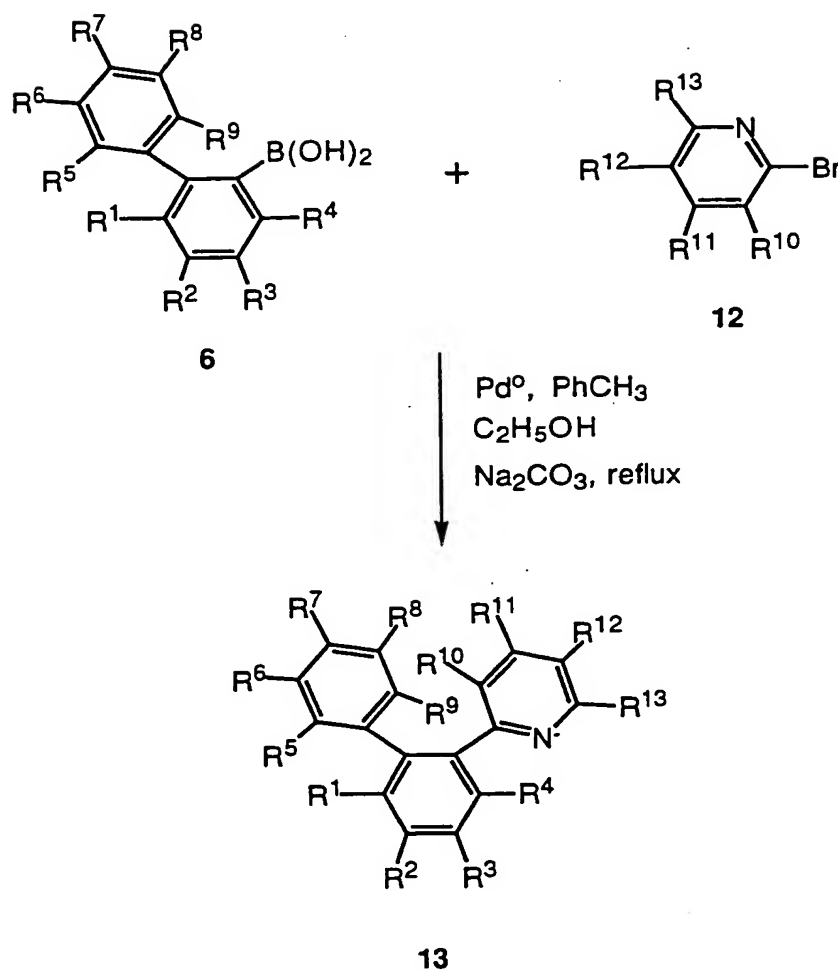
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## SCHEME XIII



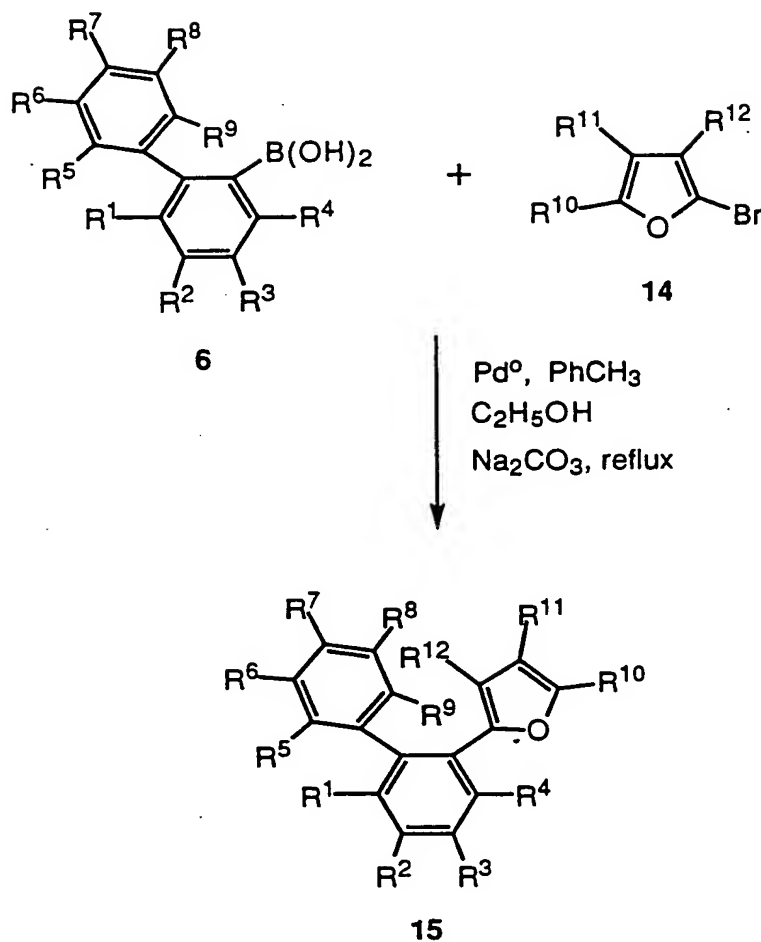
5 Synthetic Scheme XIII shows the procedure for the preparation of 1,2-diarylbenzene antiinflammatory agents 11 from 2-bromo-biphenyl intermediates 3 (prepared in Synthetic Scheme III) and the appropriate substituted pyridyltin intermediates 10 (prepared in Synthetic Scheme XII). Reaction of 3 with 10 in toluene at reflux in the presence of a Pd<sup>0</sup> catalyst, e.g., tetrakis(triphenylphosphine)palladium (0) gives the corresponding 1,2-diarylbenzene antiinflammatory agents 11 of this invention.

## SCHEME XIV



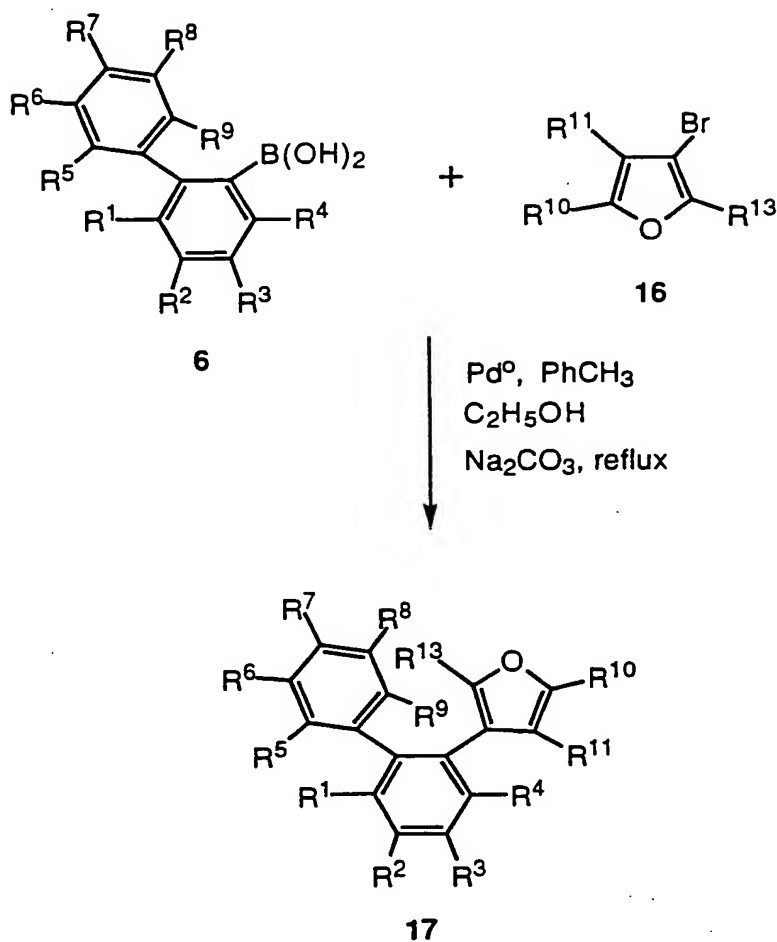
5            Synthetic Scheme XIV shows the procedure for the  
 preparation of 1,2-diarylbenzene antiinflammatory agents  
 13 from 2-aryl-phenylboronic acids 6 (prepared in  
 Synthetic Scheme VIII) and commercially available  
 bromopyridines 12. Reaction of 6 with 12 in  
 10    toluene/ethanol at reflux in the presence of a  $\text{Pd}^0$   
 catalyst, e.g., tetrakis(triphenylphosphine)palladium  
 (0) and 2M sodium carbonate gives the corresponding 1,2-  
 diarylbenzene antiinflammatory agents 13 of this  
 invention.

## SCHEME XV



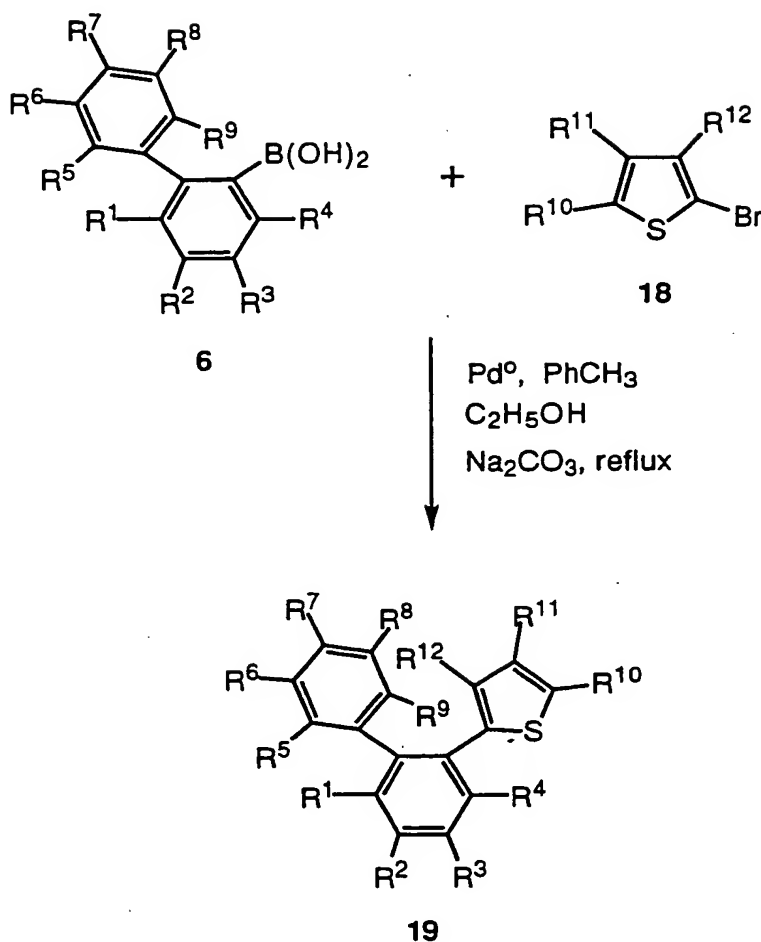
5            Synthetic Scheme XV shows the procedure for the  
 preparation of 1,2-diarylbenzene antiinflammatory agents  
 15 from 2-aryl-phenylboronic acids 6 (prepared in  
 Synthetic Scheme VIII) and commercially available 2-  
 bromofuran 14. Reaction of 6 with 14 in  
 10 toluene/ethanol at reflux in the presence of a Pd<sup>0</sup>  
 catalyst, e.g., tetrakis(triphenylphosphine)palladium  
 (0) and 2M sodium carbonate gives the corresponding 1,2-  
 diarylbenzene antiinflammatory agents 15 of this  
 invention.

## SCHEME XVI



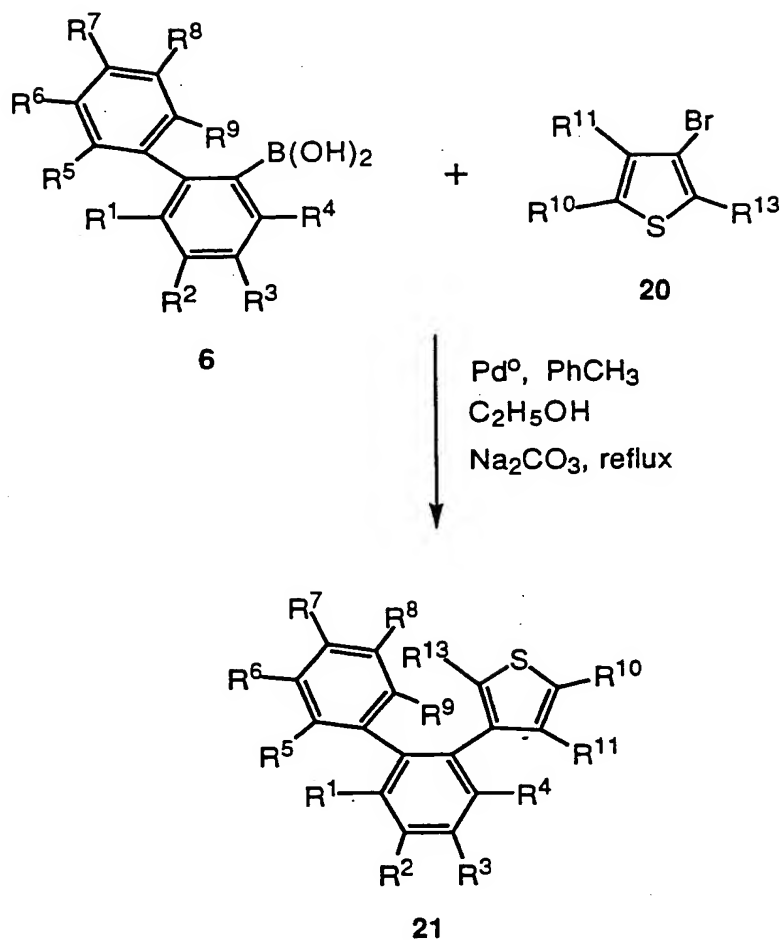
5 Synthetic Scheme XVI shows the procedure for the  
 preparation of 1,2-diarylbenzene antiinflammatory agents  
 17 from 2-aryl-phenylboronic acids 6 (prepared in  
 Synthetic Scheme VIII) and commercially available 3-  
 bromofuran 16. Reaction of 6 with 16 in  
 10 toluene/ethanol at reflux in the presence of a  $\text{Pd}^0$   
 catalyst, e.g., tetrakis(triphenylphosphine)palladium  
 (0) and 2M sodium carbonate gives the corresponding 1,2-  
 diarylbenzene antiinflammatory agents 17 of this  
 invention.

## SCHEME XVII



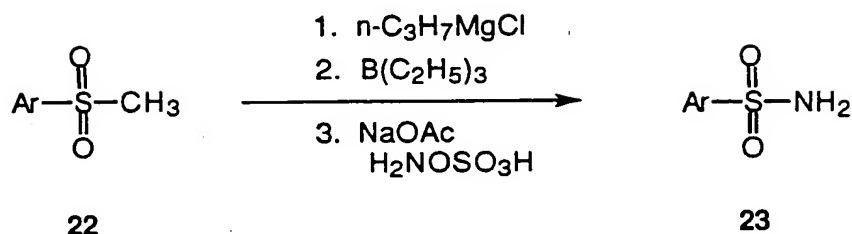
5            Synthetic Scheme XVII shows the procedure for the  
 preparation of 1,2-diarylbenzene antiinflammatory agents  
 19 from 2-aryl-phenylboronic acids 6 (prepared in  
 Synthetic Scheme VIII) and commercially available 2-  
 bromothiophene 18. Reaction of 6 with 18 in  
 10    toluene/ethanol at reflux in the presence of a Pd<sup>0</sup>  
 catalyst, e.g., tetrakis(triphenylphosphine)palladium  
 (0) and 2M sodium carbonate gives the corresponding 1,2-  
 diarylbenzene antiinflammatory agents 19 of this  
 invention.

## SCHEME XVIII



5            Synthetic Scheme XVIII shows the procedure for the  
 preparation of 1,2-diarylbenzene antiinflammatory agents  
 21 from 2-aryl-phenylboronic acids 6 (prepared in  
 Synthetic Scheme VIII) and commercially available 3-  
 bromothiophene 20. Reaction of 6 with 20 in  
 10    toluene/ethanol at reflux in the presence of a Pd<sup>0</sup>  
 catalyst, e.g., tetrakis(triphenylphosphine)palladium  
 (0) and 2M sodium carbonate gives the corresponding 1,2-  
 diarylbenzene antiinflammatory agents 21 of this  
 invention.

## SCHEME XIX



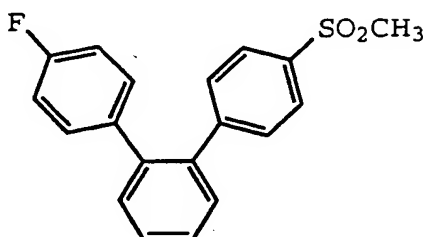
5                    Synthetic Scheme XIX shows the three step  
 procedure for the preparation of sulfonamide  
 antiinflammatory agents 23 from their corresponding  
 methyl sulfones 22. Using a procedure similar to the  
 one developed by Huang et al. [*Tetrahedron Lett.*, 35,  
 10 7201 (1994)], THF solutions of the methyl sulfones 22 at  
 -78° C are treated with base, e.g., n-BuLi, n-C<sub>3</sub>H<sub>7</sub>MgCl,  
 etc., to generate the corresponding carbanions. In step  
 two, the anions are treated with an organoborane, e.g.,  
 triethylborane, tributylborane, etc., at -78° C and  
 15 warmed to ambient temperature prior to stirring at  
 reflux. An alternative to the boron chemistry involves  
 room temperature alkylation, such as with  
 haloalkyltrialkylsilanes, followed by treatment with  
 silylalkyl-elimination agents. In step three, an  
 20 aqueous solution of sodium acetate and hydroxyamine-O-  
 sulfonic acid is added to provide the corresponding  
 sulfonamide antiinflammatory agents 23 (5 where R<sub>12</sub> =  
 SO<sub>2</sub>NH<sub>2</sub>) of this invention.

The following examples contain detailed  
 25 descriptions of the methods of preparation of compounds  
 of Formulas I-IV. These detailed descriptions fall  
 within the scope, and serve to exemplify, the above  
 described General Synthetic Procedures which form part  
 of the invention. These detailed descriptions are  
 30 presented for illustrative purposes only and are not  
 intended as a restriction on the scope of the invention.  
 All parts are by weight and temperatures are in Degrees  
 centigrade unless otherwise indicated. HRMS is an



abbreviation for High resolution mass spectrometry. The term "ND" signifies "not determined." All NMR data are from  $^1\text{H}$  NMR unless otherwise indicated.

### EXAMPLE 1



#### 1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene

##### Step 1: Preparation of 1-bromo-2-(4-fluorophenyl)benzene

Under nitrogen, 1.2 g (1.0 mmol) of  $\text{Pd}(\text{PPh}_3)_4$  was added to a stirred solution of 9.9 g (42 mmol) of 1,2-dibromobenzene (Aldrich) and 3.0 g (21 mmol) of 4-fluorophenylboronic acid in 42 mL of toluene, 42 mL of ethanol and 42 mL of 2M  $\text{Na}_2\text{CO}_3$ . After vigorous stirring at reflux for 3 hours, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate. The resulting solution was washed with water and dried over  $\text{MgSO}_4$ . Purification by silica gel chromatography (Waters Prep-500A) with hexane gave 4.35 g (81%) of 1-bromo-2-(4-fluorophenyl)benzene as a colorless oil: NMR ( $\text{CDCl}_3$ )  $\delta$  7.07-7.26 (m, 3H), 7.27-7.44 (m, 4H), 7.67 (d,  $J = 8$  Hz, 1H).

##### Step 2: Preparation of 4-methylthiophenylboronic acid

Under nitrogen, 113 mL (181 mmol) of *n*-BuLi (1.6 M in hexanes) was added to a stirred solution of 30 g (150 mmol) of 4-bromothiobenzene (Lancaster) in 1,500 mL of anhydrous tetrahydrofuran (THF) at  $-78^\circ\text{C}$ . After 30 minutes, 51 mL (450 mmol) of trimethylborate was added. The reaction was

warmed to ambient temperature and stirred overnight. The resulting solution was treated with 300 mL of 10% NaOH and stirred vigorously for 1 hour. The THF was removed in vacuo, the pH adjusted to 4-5 and the solid collected by  
5 filtration. The solid was washed repeatedly with water and hexane. Drying in vacuo gave 21 g (83%) of 4-methylthiophenylboronic acid as a colorless solid: NMR (DMSO- $d_6$ )  $\delta$  2.47 (s, 3H), 7.20 (d,  $J$  = 8 Hz, 2H), 7.71 (d,  $J$  = 8 Hz, 2H), 7.96 (s, 2H).

10

Step 3: Preparation of 1-(4-fluorophenyl)-2-[4-(methylthio)phenyl] benzene

Under nitrogen, 200 mg of  $\text{Pd}(\text{PPh}_3)_4$  was added to a stirred solution of 500 mg (2.0 mmol) of 1-bromo-2-(4-fluorophenyl)benzene (Step 1) and 500 mg (3.0 mmol) of 4-methylthiophenylboronic acid (Step 2) in 7 mL of toluene, 7  
15 mL of ethanol and 7 mL of 2M  $\text{Na}_2\text{CO}_3$ . After vigorous stirring at reflux overnight, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate. The  
20 resulting solution was washed with water and dried over  $\text{MgSO}_4$ . Purification by silica gel chromatography (Waters LC-2000) with ethyl acetate/hexane (2:98) as the eluent gave 550 mg of 1-(4-fluorophenyl)-2-[4-(methylthio)phenyl]benzene as a semi-solid: NMR ( $\text{CDCl}_3$ )  $\delta$   
25 2.46 (s, 3H), 6.92 (t,  $J$  = 8 Hz, 2H), 7.02-7.14 (m, 6H), 7.37-7.42 (m, 4H). MS (EI):  $m/e$  (rel intensity) 294 (100), 279 (39), 277 (56), 246 (74), 227 (40), 190 (43), 190 (38), 140 (44).

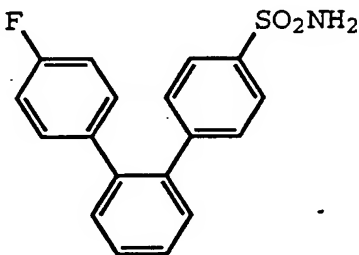
30 Step 4: Preparation of 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl] benzene

To a stirred solution of 550 mg (1.9 mmol) of crude 1-(4-fluoro-phenyl)-2-[4-(methylthio)phenyl]benzene (Step 3) in 10 mL of methylene chloride at ambient temperature was  
35 slowly added 1.3 g (4.1 mmol) of 3-chloroperoxybenzoic acid (ca. 55%). Stirring was continued for 20 minutes prior to the addition of 1 g of  $\text{Na}_2\text{SO}_3$ . The reaction was allowed to

stir for an additional 10 minutes and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and the resulting solution washed twice with saturated NaHCO<sub>3</sub> and dried over MgSO<sub>4</sub>. Recrystallization from ethyl

5 acetate/hexane gave 437 mg (94%) of 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 178.0-179.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 6.93 (t,  $J$  = 8 Hz, 2H), 7.03-7.09 (m, 2H), 7.32 (d,  $J$  = 8 Hz, 2H), 7.38-7.50 (m, 4H), 7.80 (d,  $J$  = 8 Hz, 2H). MS (FAB): m/e 333  
10 (M+Li). Anal. Calc'd for C<sub>19</sub>H<sub>15</sub>FO<sub>2</sub>S: C, 69.86; H, 4.60; F, 5.79. Found: C, 69.74; H, 4.72; F, 5.51.

## EXAMPLE 2



### 4-[2-(4-Fluorophenyl)phenyl]benzenesulfonamide

#### Step 1: Preparation of 2-(4-fluorophenyl)phenylboronic acid

Following the general procedure outlined in Synthetic Scheme VIII, 4.35 g (17.3 mmol) of 1-bromo-2-(4-fluorophenyl)benzene (Example 1, Step 1) was converted to 2-(4-fluorophenyl)phenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  4.27  
25 (s, 2H), 7.09-7.20 (m, 2H), 7.25-7.32 (m, 1H), 7.34-7.53 (m 4H), 7.90 (d,  $J$  = 8 Hz, 1H).

#### Step 2: Preparation of 4-[2-(4-fluorophenyl)phenyl]benzenesulfonamide

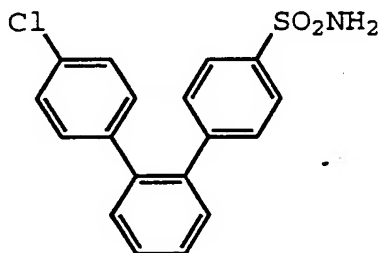
30 Following the general procedure outlined in Synthetic Scheme IX, 1.5 g (6.9 mmol) of 2-(4-fluorophenyl)phenylboronic acid (Step 1) was reacted with

2.5 g (10.4 mmol) of 4-bromobenzenesulfonamide (Lancaster). Purification by silica gel chromatography (Waters LC-2000) with ethyl acetate/hexane (3:7) and subsequent recrystallization from ethyl acetate/hexane gave 1.04 g

- 5 (46%) of 4-[2-(4-fluorophenyl)phenyl] benzenesulfonamide as a colorless solid: mp 187.3-188.2 °C; NMR (CDCl<sub>3</sub>) δ 4.83 (s, 2H), 6.92 (t, *J* = 9 Hz, 2H), 7.02-7.11 (m, 2H), 7.27 (d, *J* = 9 Hz, 2H), 7.36-7.50 (m, 4H), 7.78 (d, *J* = 8 Hz, 2H). MS (EI): m/e (rel intensity) 327 (75) 245 (100);
- 10 HRMS Calc'd for C<sub>18</sub>H<sub>14</sub>FNO<sub>2</sub>S: 327.0729. Found: 327.0743. Anal. Calc'd for C<sub>18</sub>H<sub>14</sub>FNO<sub>2</sub>S: C, 66.04; H, 4.31; N, 4.28. Found: C, 65.86; H, 4.51; N, 4.34.

### EXAMPLE 3

15



#### 4-[2-(4-Chlorophenyl)phenyl]benzenesulfonamide

- 20 Step 1: Preparation of 1-bromo-2-(4-chlorophenyl)benzene

Following the general procedure outlined in Synthetic Scheme III, 9.0 g (38 mmol) of 1,2-dibromobenzene was reacted with 3.0 g (19 mmol) of 4-chlorophenylboronic acid

25 (Lancaster). Purification by silica gel chromatography (Waters Prep-500A) with hexane gave 4.39 g (84%) of 1-bromo-2-(4-chlorophenyl)benzene as a colorless oil: NMR (CDCl<sub>3</sub>) δ 7.18-7.26 (m, 1H), 7.28-7.44 (m, 6H), 7.68 (dd, *J* = 1.5, 8 Hz, 1H).

30

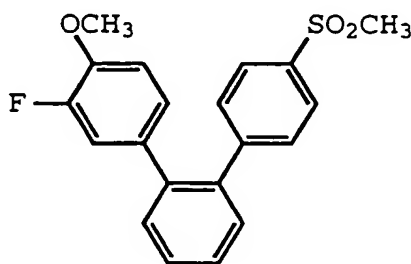
- Step 2: Preparation of 2-(4-chlorophenyl)phenylboronic acid

Following the general procedure outlined in Synthetic Scheme VIII, 4.39 g (16.4 mmol) of 1-bromo-2-(4-chlorophenyl)benzene (Step 1) was converted to 2-(4-chlorophenyl)phenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  4.20 (s, 2H), 7.19-7.55 (m, 7H), 7.89 (d,  $J$  = 8 Hz, 1H).

Step 3: Preparation of 4-[2-(4-chlorophenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme IX, 1.6 g (6.9 mmol) of 2-(4-chlorophenyl)phenylboronic acid (Step 2) was reacted with 1.8 g (7.6 mmol) of 4-bromobenzenesulfonamide. Purification by silica gel chromatography (Waters LC-2000) with ethyl acetate/hexane (3:7) and subsequent recrystallization from ethyl acetate/hexane gave 1.59 g (67%) of 4-[2-(4-chlorophenyl)phenyl] benzenesulfonamide as a colorless solid: mp 206.2-207.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  4.77 (s, 2H), 7.04 (d,  $J$  = 9 Hz, 2H), 7.16-7.31 (m, 4H), 7.36-7.51 (m, 4H), 7.80 (d,  $J$  = 9 Hz, 2H); MS (EI): m/e (rel intensity) 343 (100), 308 (13), 262 (21), 228 (82); HRMS Calc'd for C<sub>18</sub>H<sub>14</sub>ClNO<sub>2</sub>S: 343.0434. Found: 343.0434. Anal. Calc'd for C<sub>18</sub>H<sub>14</sub>ClNO<sub>2</sub>S: C, 62.88; H, 4.10; N, 4.07. Found: C, 62.66; H, 4.36; N, 4.09.

**EXAMPLE 4**



**2-Fluoro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene**

Step 1: Preparation of 1-bromo-2-[4-

(methylthio)phenylbenzene

Following the general procedure outlined in Synthetic Scheme IV, 33 g (140 mmol) of 1,2-dibromobenzene was reacted with 12 g (70 mmol) of 4-methylthiophenylboronic acid (Example 1, Step 2). Purification by silica gel chromatography with hexane gave 17.2 g (89%) of 1-bromo-2-[4-(methylthio)phenyl]benzene as a colorless oil: NMR (CDCl<sub>3</sub>)  $\delta$  2.53 (s, 3H), 7.16-7.23 (m, 1H), 7.28-7.39 (m, 6H), 7.66 (d,  $J$  = 8 Hz, 1H).

Step 2: Preparation of 1-bromo-2-[4-(methylsulfonyl)phenyl]benzene

Following the synthetic procedure outlined in Step 4 of Example 1, 17.1 g (61.3 mmol) of 1-bromo-2-[4-(methylthio)phenyl]benzene (Step 1) was oxidized to its corresponding sulfone. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (3:7) gave 16.2 g (85%) of 1-bromo-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 168.2-169.5 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.12 (s, 3H), 7.23-7.33 (m, 2H), 7.40 (dt,  $J$  = 1.5, 8 Hz, 1H), 7.61 (d,  $J$  = 8 Hz, 2H), 7.70 (dd,  $J$  = 1.5, 8 Hz, 1H), 8.01 (d,  $J$  = 9 Hz, 2H).

Step 3: Preparation of 3-fluoro-4-methoxyphenylboronic acid

Following the general procedure outlined in Synthetic Scheme I, 15 g (73 mmol) of 4-bromo-2-fluoroanisole was converted to 3-fluoro-4-methoxyphenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  3.75 (s, 3H), 6.80 (d,  $J$  = 8 Hz, 1H), 7.36-7.48 (m, 2H).

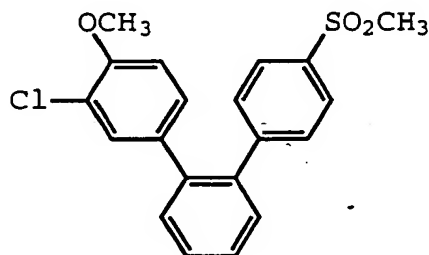
Step 4: Preparation of 2-fluoro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 5.0 g (16 mmol) of 1-bromo-2-[4-(methylsulfonyl)phenyl]benzene (Step 2) was reacted with 4.1 g (24 mmol) of 3-fluoro-4-methoxyphenylboronic acid

(Step 3). Purification by silica gel chromatography (Waters Prep- 500A) with ethyl acetate/hexane (35:65) and subsequent recrystallization from ethyl acetate/hexane gave 4.82 g (88%) of 2-fluoro-1-methoxy-4-[2-[4-

5 (methylsulfonyl)phenyl]phenyl]benzene as a colorless solid: mp 136.2-136.6 °C; NMR (CDCl<sub>3</sub>) δ 3.06 (s, 3H), 3.87 (s, 3H), 6.72-6.89 (m, 3H), 7.31-7.51 (m, 6H), 7.81 (d, *J* = 9 Hz, 2H). MS (EI): *m/e* (rel intensity) 356 (100), 262 (28), 246 (22); HRMS Calc'd for C<sub>20</sub>H<sub>17</sub>FO<sub>3</sub>S: 356.0882. Found: 10 356.0881. Anal. Calc'd for C<sub>20</sub>H<sub>17</sub>FO<sub>3</sub>S: C, 67.40; H, 4.81; F, 5.33. Found: C, 67.24; H, 4.83; F, 5.25.

## EXAMPLE 5



15

### 2-Chloro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene

#### 20 Step 1: Preparation of 4-bromo-2-chloroanisole

Under nitrogen, 7.3 mL (77 mmol) of dimethylsulfate was added to a stirred suspension of 10 g (48 mmol) of 4-bromo-2-chlorophenol and 5.4 g (38 mmol) of powdered K<sub>2</sub>CO<sub>3</sub> in 75 mL of fresh acetone. After 2 hours at reflux, the 25 reaction was cooled to ambient temperature, filtered, and concentrated in vacuo. The residue was dissolved in ethyl acetate; the resulting solution was washed with water and dried over MgSO<sub>4</sub>. Concentration in vacuo gave 10.2 g (96%) of 4-bromo-2-chloroanisole as a colorless solid: mp 68.5- 30 70.5 °C; NMR (CDCl<sub>3</sub>) δ 3.88 (s, 3H), 6.80 (d, *J* = 9 Hz, 1H), 7.33 (dd, *J* = 2, 9 Hz, 1H), 7.50 (d, *J* = 2 Hz, 1H).

Step 2: Preparation of 3-chloro-4-methoxyphenylboronic acid

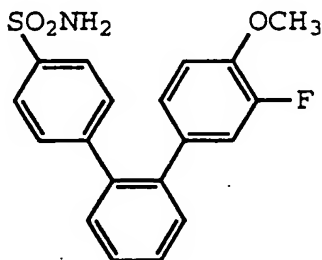
Following the general procedure outlined in Synthetic Scheme I, 10.2 g (46.2 mmol) of 4-bromo-2-chloroanisole (Step 1) was converted to 3-chloro-4-methoxyphenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  3.83 (s, 3H), 6.57 (s, 2H), 6.83 (d,  $J$  = 8 Hz, 1H), 7.64 (dd,  $J$  = 1.5, 8 Hz, 1H), 7.77 (d,  $J$  = 1.5 Hz, 1H).

10 Step 3: Preparation of 2-chloro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 4.0 g (13 mmol) of 1-bromo-2-[4-(methylsulfonyl)phenyl]benzene (Example 4, Step 2) was  
15 reacted with 2.86 g (15.4 mmol) of 3-chloro-4-methoxyphenylboronic acid (Step 2). Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (35:65) and subsequent recrystallization from ethyl acetate/hexane gave 3.31 g (69%) of 2-chloro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene as a  
20 colorless solid: mp 161.5-162.3 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 3.88 (s, 3H), 6.75 (d,  $J$  = 9 Hz, 1H), 6.87 (dd,  $J$  = 1.5, 9 Hz, 1H), 7.17 (d,  $J$  = 2 Hz, 1H), 7.34 (d,  $J$  = 9 Hz, 2H), 7.37-7.51 (m, 4H), 7.82 (d,  $J$  = 8 Hz, 2H). MS (EI):  
25 m/e (rel intensity) 372 (100), 243 (24); HRMS Calc'd for C<sub>20</sub>H<sub>17</sub>ClO<sub>3</sub>S: 372.0587. Found: 372.0557. Anal. Calc'd for C<sub>20</sub>H<sub>17</sub>ClO<sub>3</sub>S: C, 64.43; H, 4.60; Cl, 9.51. Found: C, 64.17; H, 4.56; Cl, 9.63.

30

**EXAMPLE 6**





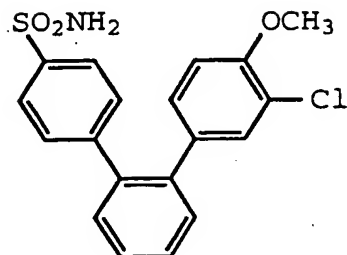
**4-[2-(3-Fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide**

5    Step 1: Preparation of 4-[2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide

Under nitrogen, 5.8 mL (9.2 mmol) of propylmagnesium chloride (1.6 M in Et<sub>2</sub>O) was added to a stirred solution of 3.0 g (8.4 mmol) of 2-fluoro-1-methoxy-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene (the title compound of Example 4, Step 4) in 9.6 mL of anhydrous tetrahydrofuran at 0 °C. The resulting solution was warmed to ambient temperature and stirred for 30 minutes. The reaction was cooled to 0 °C prior to the addition of 12.6 mL (12.6 mmol) of triethylborane (1.0 M in THF). The reaction was warmed to ambient temperature and stirred for 90 minutes prior to stirring at reflux for 40 hours. The reaction was cooled to 0 °C and treated with 6.4 g (78 mmol) of sodium acetate, 3.8 g (34 mmol) of hydroxylamine-O-sulfonic acid, and 11 mL of water; stirring was continued as the reaction slowly warmed to ambient temperature. The reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined ethyl acetate extractions were washed with brine and dried over MgSO<sub>4</sub>.

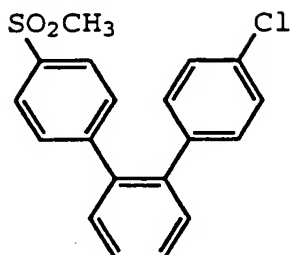
25 Purification by silica gel chromatography (Waters LC-2000) with ethyl acetate/hexane (3:7) and subsequent recrystallization from ethyl acetate/hexane gave 2.0 g (67%) of 4-[2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 143.5-145.5 °C (dec); NMR (CDCl<sub>3</sub>) δ 3.96 (s, 3H), 4.90 (s, 2H), 6.74-6.90 (m, 3H), 7.29 (d, *J* = 9 Hz, 2H), 7.35-7.48 (m, 4H), 7.79 (d, *J* = 9 Hz, 2H). MS (FAB): *m/e* 364<sup>+</sup> (M+Li); HRMS Calc'd for C<sub>19</sub>H<sub>16</sub>FNO<sub>3</sub>S: 357.0835. Found: 357.0809. Anal. Calc'd for C<sub>19</sub>H<sub>16</sub>FNO<sub>3</sub>S (0.20 ethyl acetate & 0.13 H<sub>2</sub>O) C, 63.04; H, 4.77; N, 3.71. Found: C, 63.03; H, 4.59; N, 3.52.

## EXAMPLE 7



5                                    4 - [2 - (3 - Chloro - 4 -  
methoxyphenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 2.5 g (6.7 mmol) of 2-chloro-1-methoxy-4-[2-[4-(methanesulfonyl)phenyl]phenyl]benzene (the title compound of Example 5) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (Waters LC-2000) with ethyl acetate/hexane (3:7) and subsequent recrystallization from ethyl acetate/hexane gave  
10 1.31 g (52%) of 4-[2-(3-chloro-4-methoxyphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 179.5-180.2 °C; NMR (CDCl<sub>3</sub>) δ 3.87 (s, 3H), 4.76 (s, 2H), 6.75 (d, J = 9 Hz, 1H), 6.86 (dd, J = 2, 9 Hz, 1H), 7.20 (d, J = 3 Hz, 1H), 7.29 (d, J = 9 Hz, 2H), 7.35-  
15 7.47 (m, 4H), 7.79 (d, J = 8 Hz, 2H). MS (EI): m/e (rel intensity) 373 (100), 258 (17), 243 (29); HRMS Calc'd for C<sub>19</sub>H<sub>16</sub>ClNO<sub>3</sub>S: 373.0539. Found: 373.0587. Anal. Calc'd for C<sub>19</sub>H<sub>16</sub>ClNO<sub>3</sub>S: C, 61.04; H, 4.31; N, 3.75. Found: C, 60.76; H, 4.28; N, 3.48.

**EXAMPLE 8**

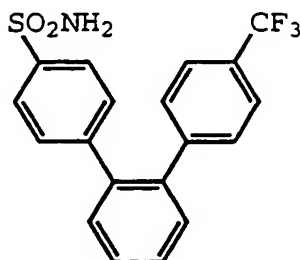
5                    **1-(4-Chlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene**

Following the general procedure outlined in Synthetic Scheme VI, 2.3 g (7.4 mmol) of 1-bromo-2-[4-

10 (methylsulfonyl)phenyl]benzene (Example 4, Step 2) was reacted with 1.7 g (11 mmol) of 4-chlorophenylboronic acid. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 1.90 g

15 (74%) of 1-(4-chlorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 180.2-180.6 °C; NMR (CDCl<sub>3</sub>) δ 3.06 (s, 3H), 7.04 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.38-7.51 (m, 4H), 7.81 (d, J = 8 Hz, 2H). MS (EI): m/e (rel intensity) 342 (34), 228 (100); HRMS Calc'd for C<sub>19</sub>H<sub>15</sub>ClO<sub>2</sub>S: 342.0481. Found: 342.0484. Anal. Calc'd for C<sub>19</sub>H<sub>15</sub>ClO<sub>2</sub>S: C, 66.56; H, 4.41; Cl, 10.34. Found: C, 66.45; H, 4.48; Cl, 10.63.

25                    **EXAMPLE 9**



**4-[2-[4-(Trifluoromethyl)phenyl]phenyl]benzenesulfonamide**

5    Step 1: Preparation of 4-(trifluoromethyl)phenylboronic acid

Following the general procedure outlined in Synthetic Scheme I, 8.9 g (39 mmol) of 4-bromobenzotrifluoride was converted to 4-(trifluoromethyl)phenylboronic acid.

10

Step 2: Preparation of 1-[4-(trifluoromethyl)phenyl]-2-[4-(methylsulfonyl)phenyl]benzene

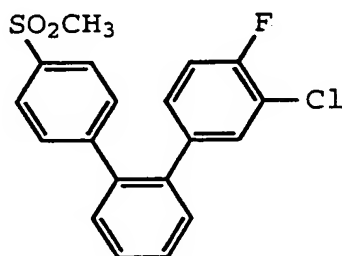
Following the general procedure outlined in Synthetic Scheme VI, 4.0 g (13 mmol) of 1-bromo-2-[4-(methylsulfonyl)phenyl]benzene (Example 4, Step 2) was reacted with 3.8 g (20 mmol) of 4-(trifluoromethyl)phenylboronic acid (Step 1). Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 3.80 g (77%) of 1-[4-(trifluoromethyl)phenyl]-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 172.8-173.5 °C; NMR (CDCl<sub>3</sub>) δ 3.06 (s, 3H), 7.23 (d, J = 8 Hz, 2H), 7.33 (d, J = 9 Hz, 2H), 7.41-7.46 (m, 2H), 7.48-7.54 (m, 4H), 7.81 (d, J = 9 Hz, 2H). MS (ES): m/e 383 (M+Li); HRMS Calc'd for C<sub>20</sub>H<sub>15</sub>F<sub>3</sub>O<sub>2</sub>S: 376.0745. Found: 376.0766.

20  
30    Step 3: Preparation of 4-[2-[4-(trifluoromethyl)phenyl]phenyl]benzenesulfonamide

Following the synthetic procedure outlined in Synthetic Scheme XI, 2.62 g (6.96 mmol) of 1-[4-(trifluoromethyl)phenyl]-2-[4-(methylsulfonyl)phenyl]benzene (Step 2) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (Water Prep-500A) with ethyl acetate/hexane (3:7) and subsequent recrystallization from ethyl

acetate/hexane gave 1.85 g (70%) of 4-[2-[4-(trifluoromethyl)phenyl]phenyl]benzenesulfonamide as a colorless solid: mp 187.5-187.8 °C; NMR (CDCl<sub>3</sub>) δ 4.79 (s, 2H), 7.20-7.31 (m, 4H), 7.38-7.54 (m, 6H), 7.80 (d, J = 8 Hz, 2H). MS (EI): m/e (rel intensity) 377 (14), 297 (25), 228 (100); HRMS Calc'd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>2</sub>S: 377.0697. Found: 377.0737. Anal. Calc'd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>2</sub>S: C, 60.47; H, 3.74; N, 3.71. Found: C, 60.43; H, 3.97; N, 3.48.

## EXAMPLE 10



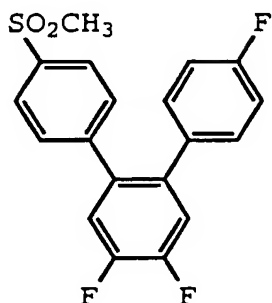
### 2-Chloro-1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene

Step 1: Preparation of 2-chloro-1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 6.43 g (20.6 mmol) of 1-bromo-2-[4-(methylsulfonyl)phenyl]benzene (Example 4, Step 2) was reacted with 5.37 g (30.9 mmol) of 3-chloro-4-fluorophenylboronic acid. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) gave 6.64 g (89%) of 2-chloro-1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]phenyl]benzene as a colorless solid: mp 179.5-181.1 °C; NMR (CDCl<sub>3</sub>) δ 3.06 (s, 3H), 6.86-6.93 (m, 1H), 6.98 (t, J = 8 Hz, 1H), 7.19 (dd, J = 2, 7 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 7.38-7.53 (m, 4H), 7.84 (d, J = 9 Hz, 2H). MS (FAB): m/e 367 (M+Li); HRMS Calc'd for C<sub>19</sub>H<sub>14</sub>ClFO<sub>2</sub>S: 360.0387. Found: 360.0401. Anal. Calc'd

for C<sub>19</sub>H<sub>14</sub>ClFO<sub>2</sub>S: C, 63.25; H, 3.91; F, 5.27. Found: C, 62.92; H, 4.02; F, 5.19.

### EXAMPLE 11



#### 1,2-Difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene

##### Step 1: Preparation of 1,2-difluoro-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]benzene

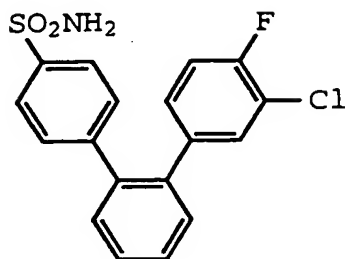
Under nitrogen, 3 g (2.6 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to a stirred solution of 5.0 g (18 mmol) of 1,2-dibromo-4,5-difluorobenzene (Aldrich), 4.2 g (25 mmol) of 4-methylthiophenylboronic acid (Example 1, Step 2), and 3.1 g (22 mmol) of 4-fluorophenylboronic acid in 100 mL of toluene, 100 mL of ethanol, and 100 mL of 2M Na<sub>2</sub>CO<sub>3</sub>. After vigorous stirring at reflux overnight, the solvent was removed in vacuo and the residue dissolved in ethyl acetate. The resulting solution was washed with water and dried over MgSO<sub>4</sub>. Purification by silica gel chromatography gave 1,2-difluoro-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]benzene as a semi-solid which was used without further purification.

##### Step 2: Preparation of 1,2-difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene

To a stirred solution of 6.34 g (ca. 18 mmol) of the crude 1,2-difluoro-4-(4-fluorophenyl)-5-[4-

(methylthio)phenyl]benzene (Step 1) in 125 mL of methylene chloride at 0 °C was slowly added 14.6 g (54 mmol) of 3-chloroperoxybenzoic acid (ca 64%); after stirring for 90 minutes, the reaction was diluted with additional methylene chloride, washed with 3 times with 5% NaOH, and dried over MgSO<sub>4</sub>. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 2.81 g (43%) of 1,2-difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 172.8-173.5 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 6.94 (t,  $J$  = 8 Hz, 2H), 6.98-7.06 (m, 2H), 7.21-7.31 (m, 4H), 7.81 (d,  $J$  = 8 Hz, 2H). MS (FAB):  $m/e$  369 (M+Li); HRMS Calc'd for C<sub>19</sub>H<sub>13</sub>F<sub>3</sub>O<sub>2</sub>S: 362.0588. Found: 362.0586. Anal. Calc'd for C<sub>19</sub>H<sub>13</sub>F<sub>3</sub>O<sub>2</sub>S: C, 62.98; H, 3.62; F, 15.73. Found: C, 62.96; H, 3.70; F, 15.76.

## EXAMPLE 12



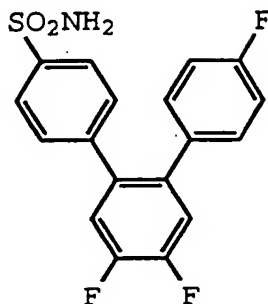
5

4-[2-(3-Chloro-4-  
fluorophenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 5.0 g (14 mmol) of 2-chloro-1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]phenyl]benzene (the title compound of Example 10) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (28:72) and subsequent recrystallization from ethyl acetate/hexane gave 1.47 g (29%) of 4-[2-(3-chloro-4-fluorophenyl)phenyl]benzenesulfonamide as a colorless solid: mp 192.5-193.2 °C; NMR (CDCl<sub>3</sub>) δ 6.36 (s, 2H), 6.68-6.76 (m, 1H), 6.81 (t, J = 9 Hz, 1H), 7.06 (d, J = 8 Hz, 2H), 7.17-7.32 (m, 5H), 7.63 (d, J = 8, 2H). MS (FAB): m/e 368 (M+Li); HRMS Calc'd for C<sub>18</sub>H<sub>13</sub>ClFNO<sub>2</sub>S: 361.0340. Found: 361.0338. Anal. Calc'd for C<sub>18</sub>H<sub>13</sub>ClFNO<sub>2</sub>S: C, 59.75; H, 3.62; N, 3.87. Found: C, 59.80; H, 3.91; N, 4.05.



## EXAMPLE 13

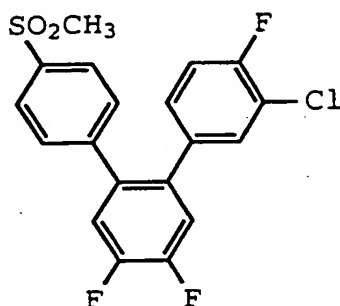


5

4-[3,4-Difluoro-6-(4-fluorophenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 2.65 g (7.32 mmol) of 1,2-difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene (the title compound of Example 11) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (Waters LC-2000) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 1.37 g (52%) of 4-[3,4-difluoro-6-(4-fluorophenyl)phenyl]benzenesulfonamide as a colorless solid: mp 190.2-191.5 °C; NMR (CDCl<sub>3</sub>) δ 4.77 (s, 2H), 6.94 (t,  $J$  = 8 Hz, 2H), 6.98-7.06 (m, 2H), 7.17-7.28 (m, 4H), 7.79 (d,  $J$  = 8 Hz, 2H). MS (FAB):  $m/e$  370 (M+Li); HRMS Calc'd for C<sub>18</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>2</sub>S: 363.0541. Found: 363.0576. Anal. Calc'd for C<sub>18</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>2</sub>S: C, 59.50; H, 3.33; N, 3.85. Found: C, 59.52; H, 3.57; N, 3.68.

## EXAMPLE 14



5      1-(3-Chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene

Step 1: Preparation of 1-(3-chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylthio)phenyl]benzene

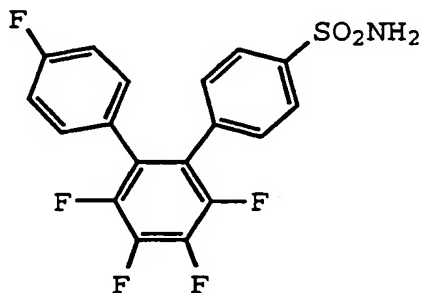
10      Following the general procedure outlined in Synthetic Scheme VII, 4.1 g (15 mmol) of 1,2-dibromo-4,5-difluorobenzene, 3.0 g (18 mmol) of 4-methylthiophenylboronic acid (Example 1, Step 2) and 2.9 g (16.5 mmol) of 3-chloro-4-fluorophenylboronic acid were  
15      reacted. Purification by silica gel chromatography gave 3.5 g of 1-(3-chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylthio)phenyl]benzene as a semi-solid which was used without further purification.

20      Step 2: Preparation of 1-(3-chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene

Following the synthetic procedure outlined in Step 2 of Example 11, 3.50 g (ca. 15 mmol) of crude 1-(3-chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylthio)phenyl]benzene  
25      (Step 1) was oxidized to its corresponding sulfonamide. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 1.66 g  
30      (28%) of 1-(3-chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp

172.2-172.5 °C; NMR (CDCl<sub>3</sub>) δ 3.05 (s, 3H), 6.82-6.89 (m, 1H), 6.99 (t,  $J$  = 9 Hz, 1H), 7.14 (dd,  $J$  = 2, 8 Hz, 1H), 7.20-7.32 (m, 4H), 7.84 (d,  $J$  = 8 Hz, 2H); MS (EI):  $m/e$  (rel intensity) 396 (22), 317 (12), 282 (100), 262 (25), 243 (10); HRMS Calc'd for C<sub>19</sub>H<sub>12</sub>ClF<sub>3</sub>O<sub>2</sub>S: 396.0199. Found: 396.0203. Anal. Calc'd for C<sub>19</sub>H<sub>12</sub>ClF<sub>3</sub>O<sub>2</sub>S: C, 57.51; H, 3.05; F, 14.36. Found: C, 57.31; H, 2.99; F, 14.48.

### EXAMPLE 15



#### 4-[2,3,4,5-Tetrafluoro-6-(4-fluorophenyl)phenyl]benzenesulfonamide

##### Step 1: Preparation of 1,2,3,4-tetrafluoro-5-(4-fluorophenyl)-6-[4-(methylthio)phenyl]benzene

Under nitrogen, 1 g of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to a stirred solution of 4.85 g (15.8 mmol) of 1,2-dibromo-3,4,5,6-tetrafluorobenzene (Aldrich), 2.65 g (18.9 mmol) of 4-fluorophenylboronic acid, and 3.17 g (18.9 mmol) of 4-methylthiophenylboronic acid (Example 1, Step 2) in 80 mL of toluene, 50 mL of ethanol, and 35 mL of 2M Na<sub>2</sub>CO<sub>3</sub>.

After vigorous stirring at reflux overnight, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed water, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo gave 7.3 g of 1,2,3,4-tetrafluoro-5-(4-fluorophenyl)-6-[4-(methylthio)phenyl]benzene as a yellow oil which was used without further purification.

##### Step 2: Preparation of 1,2,3,4-tetrafluoro-5-(4-

fluorophenyl)-6-[4-  
(methylsulfonyl)phenyl]benzene

To a stirred solution of 7.3 g of crude 1,2,3,4-tetrafluoro-5-(4-fluorophenyl)-6-[4-

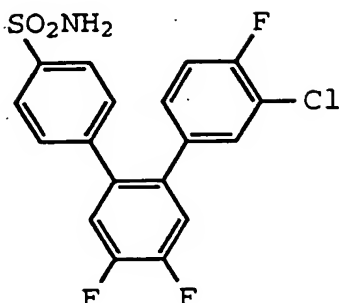
- 5 (methylthio)phenyl]benzene (Step 1) in 40 mL of methylene chloride was slowly added 15 g (43.5 mmol) of 3-chloroperoxybenzoic acid (ca. 55%) at -10 °C. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:5) followed by reversed phase  
10 chromatography (Waters DeltaPrep-3000) with acetonitrile/water/TFA (48:52:0.05) gave 1.2 g (19% overall for both steps) of 1,2,3,4-tetrafluoro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 134.0-135.0 °C; NMR (CDCl<sub>3</sub>) δ 3.05 (s, 3H), 6.91-7.03  
15 (m, 4H), 7.26 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H). MS (FAB): m/e 405 (M+Li); HRMS Calc'd for C<sub>19</sub>H<sub>11</sub>F<sub>5</sub>O<sub>2</sub>S: 398.0400, found: 398.0393.

Step 3: Preparation of 4-[2,3,4,5-tetrafluoro-6-(4-  
20 fluorophenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 1.1 g (2.76 mmol) of 1,2,3,4-tetrafluoro-5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]benzene (Step 2) was converted to its corresponding sulfonamide.

- 25 Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:5) gave 80 mg (7%) 4-[2,3,4,5-tetrafluoro-6-(4-fluorophenyl)phenyl]benzenesulfonamide as a colorless solid: mp 202.0-203.0 °C; NMR (CDCl<sub>3</sub>) δ 4.78 (br s, 2H), 6.92-7.04 (m, 4H), 7.21 (d, J = 8.5 Hz, 2H),  
30 7.82 (d, J = 8.5 Hz, 2H). MS (FAB): m/e 406 (M+Li). Anal. Calc'd for C<sub>18</sub>H<sub>10</sub>F<sub>5</sub>NO<sub>2</sub>S·(0.16 H<sub>2</sub>O): C, 53.76; H, 2.59; N, 3.48. Found: C, 53.73; H, 2.40; N, 3.44.

## EXAMPLE 16

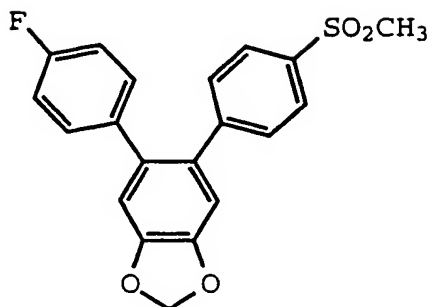


5

4-[2-(3-Chloro-4-fluorophenyl)-4,5-  
difluorophenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 2.00 g (5.04 mmol) of 1-(3-chloro-4-fluorophenyl)-4,5-difluoro-2-[4-(methanesulfonyl)phenyl]benzene (the title compound of Example 14) was converted to its corresponding sulfonamide. Purification by reverse phase chromatography (Waters DeltaPrep-3000) with acetonitrile/ water/TFA (48:52:0.05) and subsequent recrystallization from ethyl acetate/hexane gave 500 mg (25%) of 4-[2-(3-chloro-4-fluorophenyl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 162.5-162.8 °C; NMR (CDCl<sub>3</sub>) δ 4.80 (s, 2H), 6.81-6.88 (m, 1H), 6.99 (t, J = 9 Hz, 1H), 7.15-7.28 (m, 5H), 7.83 (d, J = 8 Hz, 2H). MS (FAB): m/e 404 (M+Li); HRMS Calc'd for C<sub>18</sub>H<sub>11</sub>ClF<sub>3</sub>NO<sub>2</sub>S: 397.0151. Found: 397.0152. Anal. Calc'd for C<sub>18</sub>H<sub>11</sub>ClF<sub>3</sub>NO<sub>2</sub>S: C, 54.35; H, 2.79; N, 3.52. Found: C, 54.57; H, 3.00; N, 3.42.

## EXAMPLE 17



5        **5-(4-Fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-**  
         **1,3-benzodioxole**

Step 1: 5-(4-fluorophenyl)-6-[4-(methylthio)phenyl]-  
         1,3-benzodioxole

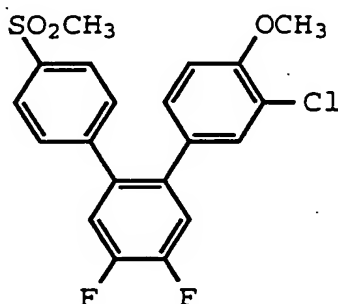
10        Under nitrogen, 1 g of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to a  
stirred solution of 4 g (14.3 mmol) of 5,6-dibromo-1,3-  
benzodioxole (Lancaster), 2.4 g (17.2 mmol) of 4-  
fluorophenylboronic acid, and 2.87 g (17.2 mmol) of 4-  
methylthiophenylboronic acid (Example 1, Step 2) in 70 mL  
15        of toluene, 40 mL of ethanol, and 30 mL of 2M Na<sub>2</sub>CO<sub>3</sub>.  
After vigorous stirring at reflux overnight, the solvent  
was removed in vacuo. The residue was dissolved in ethyl  
acetate, washed with water, and dried over Na<sub>2</sub>SO<sub>4</sub>.  
Concentration in vacuo gave 6.9 g of 5-(4-fluorophenyl)-6-  
20        [4-(methylthio)phenyl]-1,3-benzodioxole as a semi-solid  
which was used without further purification.

Step 2: Preparation of 5-(4-fluorophenyl)-6-[4-  
         (methylsulfonyl)phenyl]-1,3-benzodioxole

25        To a stirred solution of 6.9 g of 5-(4-fluorophenyl)-  
6-[4-(methylthio)phenyl]-1,3-benzodioxole (Step 1) in 30 mL  
of methylene chloride was slowly added 12 g (38.2 mmol) of  
3-chloroperoxybenzoic acid (ca. 55%) at -10 °C.  
Purification by silica gel chromatography (MPLC) with ethyl  
30        acetate/hexane (1:4) followed by reversed phase  
chromatography (Waters DeltaPrep-3000) with

acetonitrile/water/TFA (45:55:0.05) gave 200 mg (4% overall for both steps) of 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]-1,3-benzodioxole as a colorless solid: mp 173.0-174.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.04 (s, 3H), 6.06 (s, 2H), 6.86-6.92 (m, 4H), 6.96-7.03 (m, 2H), 7.23-7.27 (m, 2H), 7.76 (d,  $J$  = 8.5 Hz, 2H). MS (FAB): m/e 377 (M+Li); HRMS Calc'd for C<sub>20</sub>H<sub>15</sub>FO<sub>4</sub>S: 370.0675, found: 370.0680. Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>FO<sub>4</sub>S (0.25 H<sub>2</sub>O): C, 64.08; H, 4.17. Found: C, 64.08; H, 4.15.

### EXAMPLE 18



#### 15 1-(3-Chloro-4-methoxyphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene

##### Step 1: Preparation of 1-bromo-4,5-difluoro-2-[4-(methylthio)phenyl]benzene

20 Following the general procedure outlined in Synthetic Scheme IV, 40 g (147 mmol) of 1,2-dibromo-4,5-difluorobenzene was reacted with 12.3 g (73 mmol) of 4-methylthiophenylboronic acid (Example 1, Step 2). Purification by silica gel chromatography with hexane gave 25 40.3 g of 1-bromo-4,5-difluoro-2-[4-(methylthio)phenyl]benzene as a yellow oil which was used without further purification.

##### Step 2: Preparation of 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene

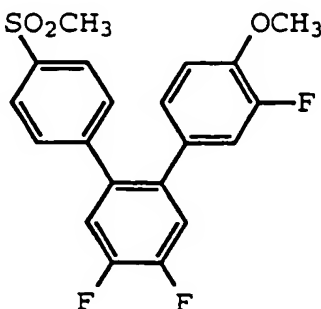
30 Following the synthetic procedure outlined in Step 4 of Example 1, 40.3 g (ca. 73 mmol) of 1-bromo-4,5-difluoro-

2-[4-(methylthio)phenyl]benzene (Step 1) was oxidized to its corresponding sulfone. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) gave 17.4 g (68%) of 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 158.5-159.5 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.12 (s, 3H), 7.13-7.21 (m, 1H), 7.50-7.60 (m, 3H), 8.02 (d,  $J$  = 9 Hz, 2H).

Step 3: Preparation of 1-(3-chloro-4-methoxyphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 4.4 g (13 mmol) of 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Step 2) was reacted with 3.1 g (17 mmol) of 3-chloro-4-methoxy phenylboronic acid (Example 5, Step 2). Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (3:7) and subsequent recrystallization from ethyl acetate/hexane gave 4.47 g (95%) of 1-(3-chloro-4-methoxyphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 147.5-148.5 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 3.88 (s, 3H), 6.75 (d,  $J$  = 9 Hz, 1H), 6.83 (dd,  $J$  = 2, 9 Hz, 1H), 7.10 (d,  $J$  = 2 Hz, 1H), 7.17-7.32 (m, 4H), 7.83 (d,  $J$  = 9 Hz, 2H). MS (EI): m/e (rel intensity) 408 (33), 314 (15), 294 (52), 279 (63), 251 (100). Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>ClF<sub>2</sub>O<sub>3</sub>S (0.27 ethyl acetate): C, 58.53; H, 3.99; F, 8.79. Found: C, 58.75; H, 3.71; F, 8.52.

### EXAMPLE 19

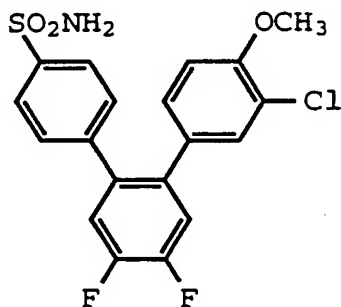




**1,2-Difluoro-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methanesulfonyl)phenyl]benzene**

- 5        Following the general procedure outlined in Synthetic Scheme VI, 3.0 g (8.6 mmol) of 1-bromo-4,5-difluoro-2-[4-(methanesulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 1.9 g (11 mmol) of 3-fluoro-4-methoxyphenylboronic acid (Example 4, Step 3).
- 10      Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 3.19 g (94%) of 1,2-difluoro-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methanesulfonyl)phenyl]benzene as a colorless solid: mp
- 15      159.2-159.7 °C; NMR (CDCl<sub>3</sub>) δ 3.05 (s, 3H), 3.87 (s, 3H), 6.63-6.85 (m, 3H), 7.16-7.32 (m, 4H), 7.82 (d, J = 8 Hz, 2H). MS (EI): m/e (rel intensity) 392 (49), 313 (15), 298 (48), 269 (100), 249 (79). Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>F<sub>3</sub>O<sub>3</sub>S (0.26 ethyl acetate): C, 60.85; H, 4.15; F, 13.71. Found:
- 20      C, 61.33; H, 3.90; F, 13.40.

**EXAMPLE 20**

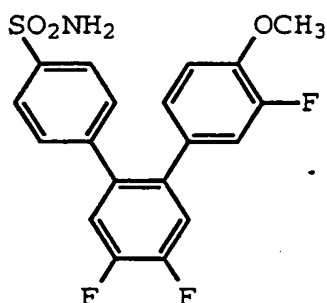


**4-[2-(3-Chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide**

- 25        Following the general procedure outlined in Synthetic Scheme XI, 4.00 g (9.78 mmol) of 1-(3-chloro-4-methoxyphenyl)-4,5-difluoro-2-[4-(methanesulfonyl)phenyl]benzene (the title compound of
- 30

Example 18) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 0.86 g (21%) of 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 70 °C (dec); NMR (CDCl<sub>3</sub>) δ 3.87 (s, 3H), 4.84 (s, 2H), 6.75 (d, *J* = 9 Hz, 1H), 6.82 (dd, *J* = 2, 9 Hz, 1H), 7.14 (d, *J* = 2 Hz, 1H), 7.16-7.28 (m, 4H), 7.81 (d, *J* = 8, 2H). MS (EI): *m/e* (rel intensity) 409 (22), 294 (15), 279 (28), 251 (100), 231 (20). Anal. Calc'd for C<sub>19</sub>H<sub>14</sub>ClF<sub>2</sub>NO<sub>3</sub>S: C, 55.68; H, 3.44; N, 3.42. Found: C, 55.42; H, 3.48; N, 3.33.

## EXAMPLE 21



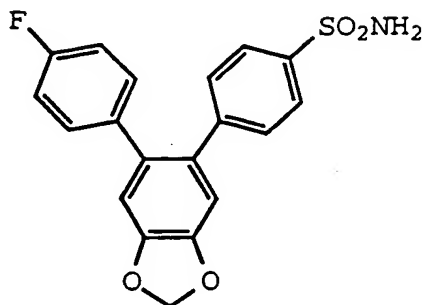
### 4-[4,5-Difluoro-2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide

20

Following the general procedure outlined in Synthetic Scheme XI, 2.50 g (6.38 mmol) of 1,2-difluoro-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methyl-sulfonyl)phenyl]benzene (the title compound of Example 19) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:3) and subsequent recrystallization from ethyl acetate/hexane gave 0.82 g (33%) of 4-[4,5-difluoro-2-(3-fluoro-4-methoxyphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 132.2-132.8 °C; NMR (CDCl<sub>3</sub>) δ 3.87 (s, 3H), 4.85 (s, 2H), 6.71-6.85 (m, 3H), 7.15-7.27 (m, 4H), 7.81 (d, *J* = 9 Hz, 2H). MS (EI): *m/e* (rel intensity) 393 (32), 298

(21), 282 (25), 269 (100), 249 (46). Anal. Calc'd for  $C_{19}H_{14}F_3NO_3S$ : C, 58.01; H, 3.59; N, 3.56. Found: C, 57.75; H, 3.48; N, 3.48.

5

**EXAMPLE 22**

10

**4-[6-(4-Fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide**

Step 1: Preparation of 5-bromo-6-(4-fluorophenyl)-1,3-benzodioxole

Under nitrogen, 1.1 g of  $Pd(PPh_3)_4$  was added to a stirred solution of 10.4 g (37.2 mmol) of 5,6-dibromo-1,3-benzodioxole and 2.6 g (18.6 mmol) of 4-fluorophenylboronic acid in 100 mL of toluene, 60 mL of ethanol, and 40 mL of 2M  $Na_2CO_3$ . After vigorous stirring at reflux overnight, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed with water, and dried over  $Na_2SO_4$ . Purification by silica gel chromatography (Waters Prep-500A) with hexane as the eluent gave 3.9 g (71%) of 5-bromo-6-(4-fluorophenyl)-1,3-benzodioxole as a colorless solid: mp 86.0-87.5 °C; NMR ( $CDCl_3$ )  $\delta$  6.02 (s, 2H), 6.77 (s, 1H), 7.04-7.13 (m, 3H), 7.28-7.35 (m, 2H).

Step 2: Preparation of [6-(4-fluorophenyl)-1,3-benzodioxol-5-yl]boronic acid

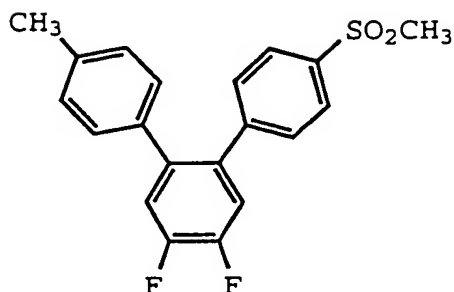
Under nitrogen, 6.3 mL (15.8 mmol) of n-BuLi (2.5 M in hexanes) was added to a stirred solution of 3.9 g (13.2 mmol) of 5-bromo-6-(4-fluorophenyl)-1,3-benzodioxole (Step

1) in 30 mL of anhydrous THF at -78 °C. After 30 minutes, 4.5 mL (39.4 mmol) of trimethylborate was added. The reaction was warmed to ambient temperature and stirred for 3 hours prior to the addition of 60 mL of 5% NaOH. The reaction was stirred for an additional 60 minutes, the THF removed in vacuo, and the pH adjusted to ca. 4. The residue was dissolved in ethyl acetate; the resulting solution was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give 1.7 g (50%) of [6-(4-fluorophenyl)-1,3-benzodioxol-5-yl]boronic acid as a pale yellow solid: NMR (CDCl<sub>3</sub>) δ 4.00 (br s, 2H), 6.06 (s, 2H), 6.75 (s, 1H), 7.08-7.17 (m, 2H), 7.26 (s, 1H), 7.31-7.39 (m, 2H).

Step 3: Preparation of 4-[6-(4-fluorophenyl)-1,3-benzodioxol-5-yl] benzenesulfonamide

Under nitrogen, 500 mg of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to a stirred solution of 1.55 g (6.0 mmol) of [6-(4-fluorophenyl)-1,3-benzodioxol-5-yl]boronic acid (Step 2) and 1.09 g (4.62 mmol) of 4-bromobenzenesulfonamide (Lancaster) in 30 mL of toluene, 20 mL of ethanol, and 15 mL of 2M Na<sub>2</sub>CO<sub>3</sub>. After vigorous stirring at reflux for 6 hours, the solvent was removed in vacuo and the residue dissolved in ethyl acetate. The resulting solution was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 1.3 g (76%) of 4-[6-(4-fluorophenyl)-1,3-benzodioxol-5-yl]benzenesulfonamide as a colorless solid: mp 191.0-192.5 °C; NMR (CDCl<sub>3</sub>) δ 4.80 (s, 2H), 6.06 (s, 2H), 6.83-6.92 (m, 4H), 6.97-7.06 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H). MS (FAB): *m/e* 372 (M+H). Anal. Calc'd for C<sub>19</sub>H<sub>14</sub>FNO<sub>4</sub>S: C, 61.45; H, 3.80; N, 3.77. Found: C, 61.48; H, 3.92; N, 3.68.

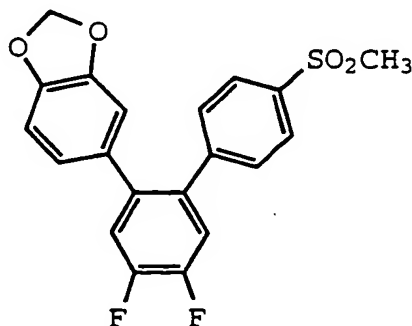
## EXAMPLE 23



5                   1,2-Difluoro-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 2.56 g (7.37 mmol) of 1-bromo-4,5-difluoro-2-  
 10 [(4-methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 1.35 g (9.93 mmol) of 4-methylphenylboronic acid. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 2.55 g (97%) of 1,2-difluoro-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp  
 15 147.0-148.0 °C; NMR (CDCl<sub>3</sub>) δ 2.32 (s, 3H), 3.05 (s, 3H), 6.92 (d, J = 8 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 7.17-7.32 (m, 4H), 7.79 (d, J = 8 Hz, 2H). MS (FAB): m/e 365 (M+Li). Anal. Calc'd for C<sub>20</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub>S: C, 67.03; H, 4.50.  
 20 Found: C, 67.18; H, 4.48.

## EXAMPLE 24



**5-[4,5-Difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-1,3-benzodioxole**

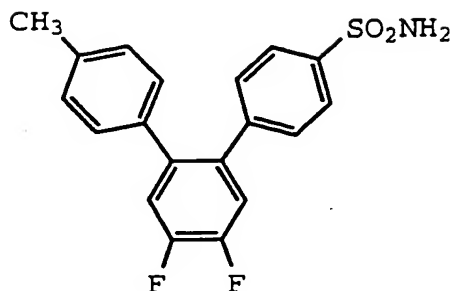
**Step 1: Preparation of (1,3-benzodioxol-5-yl)boronic acid**

Following the synthetic procedure outlined in Step 2 of Example 1, 15.2 g (75.6 mmole) of 5-bromo-1,3-benzodioxole (Aldrich) was converted to (1,3-benzodioxol-5-yl)boronic acid as a colorless solid: NMR (CDCl<sub>3</sub>)  $\delta$  5.98 (s, 2H), 6.88 (t,  $J$  = 8 Hz, 1H), 7.26-7.41 (m, 2H), 7.80 (br s, 2H).

**Step 2: Preparation of 5-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-1,3-benzodioxole**

Following the general procedure outlined in Synthetic Scheme I, 2.24 g (6.45 mmol) of 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 1.39 g (8.38 mmol) of (1,3-benzodioxol-5-yl)boronic acid (Step 1). Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:4) gave 2.47 g (99%) of 5-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-1,3-benzodioxole as a colorless solid: mp 110.0-111.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 5.95 (s, 2H), 6.47-6.52 (m, 2H), 6.67 (d,  $J$  = 8.5 Hz, 1H), 7.16-7.24 (m, 2H), 7.32 (d,  $J$  = 8.5 Hz, 2H), 7.82 (d,  $J$  = 8.5 Hz, 2H). MS (FAB):  $m/e$  395 (M+Li). Anal. Calc'd for C<sub>20</sub>H<sub>14</sub>F<sub>2</sub>O<sub>4</sub>S: C, 61.85; H, 3.63. Found: C, 61.92; H, 3.66.

## EXAMPLE 25

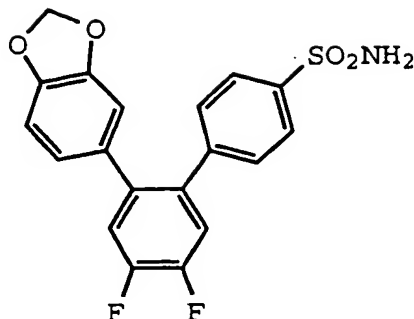


5                   4-[4,5-Difluoro-2-(4-methylphenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 2.43 g (6.78 mmol) of 1,2-difluoro-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (the title compound of Example 23) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:5) gave 1.90 g (78%) of 4-[4,5-difluoro-2-(4-methylphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 103.0-104.0 °C; NMR (CDCl<sub>3</sub>) δ 2.32 (s, 3H), 4.81 (s, 2H), 6.93 (d, J = 8 Hz, 2H), 7.04 (d, J = 8 Hz, 2H), 7.16-7.29 (m, 4H), 7.78 (d, J = 8.5 Hz, 2H). MS (EI): m/e 359 (26), 279 (33), 278 (41), 264 (100), 251 (36), 119 (62), 80 (70), 64 (56). Anal. Calc'd for C<sub>19</sub>H<sub>15</sub>F<sub>2</sub>NO<sub>2</sub>S: C, 63.50; H, 4.21; N, 3.90. Found: C, 63.55; H, 4.24; N, 3.80.

## EXAMPLE 26

92



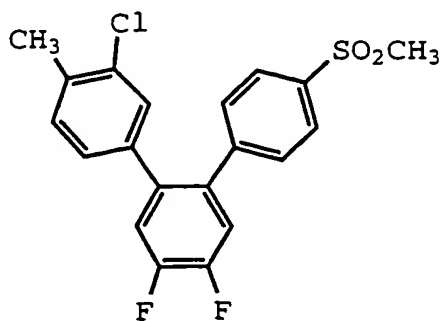
**4-[2-(1,3-Benzodioxol-5-yl)-4,5-difluorophenyl]benzenesulfonamide**

5

Following the general procedure outlined in Synthetic Scheme XI, 2.34 g (6.02 mmol) of 5-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-1,3-benzodioxole (the title compound of Example 24) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 1.84 g (78%) of 4-[2-(1,3-benzodioxol-5-yl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 142.0-143.0 °C; NMR (CDCl<sub>3</sub>) δ 4.83 (s, 2H), 5.95 (s, 2H), 6.49-6.54 (m, 2H), 6.69 (d,  $J$  = 8 Hz, 1H), 7.15-7.30 (m, 4H), 7.81 (d,  $J$  = 8 Hz, 2H). MS (EI): m/e 389 (18), 308 (14), 251 (100), 231 (43). Anal. Calc'd for C<sub>19</sub>H<sub>13</sub>F<sub>2</sub>NO<sub>4</sub>S·(0.19 H<sub>2</sub>O): C, 58.09; H, 3.43; N, 3.57. Found: C, 58.11; H, 3.51; N, 3.48.

20

**EXAMPLE 27**





**1-(3-Chloro-4-methylphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene**

**Step 1: Preparation of 3-chloro-4-methylphenylboronic acid**

5                   Following the general procedure outlined in Synthetic Scheme I, 11.1 g (54 mmol) of 4-bromo-2-chlorotoluene was converted to 3-chloro-4-methylphenylboronic acid as a colorless solid: NMR (CDCl<sub>3</sub>)  $\delta$  2.47 (s, 3H), 7.37 (d,  $J$  = 8 Hz, 1H), 7.98 (d,  $J$  = 8 Hz, 1H), 8.08 (s, 1H).

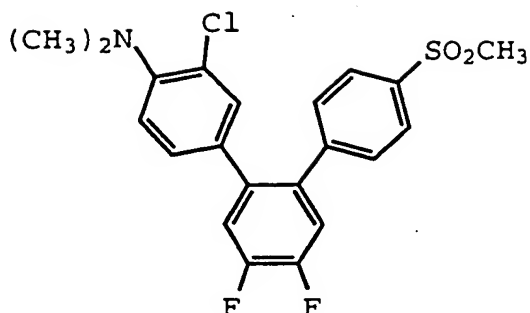
**Step 2: Preparation of 1-(3-chloro-4-methylphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene**

15                   Following the general procedure outlined in Synthetic Scheme VI, 2.49 g (7.17 mmol) of 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 1.59 g (9.33 mmol) of 3-chloro-4-methylphenylboronic acid (Step 1). Purification by silica  
20 gel chromatography (MPLC) with ethyl acetate/hexane (1:5) gave 2.65 g (94%) of 1-(3-chloro-4-methylphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 138.0-139.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.34 (s, 3H), 3.05 (s, 3H), 6.75 (dd,  $J$  = 2, 8 Hz, 1H), 7.03-7.10 (m, 2H), 7.18-7.26 (m, 2H), 7.29 (d,  $J$  = 8 Hz, 2H), 7.83 (d,  $J$  = 8 Hz, 2H). MS (FAB): m/e 399 (M+Li). Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>ClF<sub>2</sub>O<sub>2</sub>S: C, 61.15; H, 3.85. Found: C, 61.12; H, 3.82.

30

**EXAMPLE 28**

94



2-Chloro-4-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-N,N-dimethylaniline

Step 1: Preparation of 4-bromo-2-chloro-N,N-dimethylaniline

Under nitrogen, 11.6 mL (186 mmol) of iodomethane was added to a stirred solution of 12.8 g (62 mmol) of 4-bromo-2-chloroaniline and 42.8 g (310 mmol) of powdered  $K_2CO_3$  in 200 mL of DMF. Purification by silica gel chromatography (Waters Prep-500A) with ethyl acetate/hexane (5:95) gave 11.3 g (78%) of 4-bromo-2-chloro-N,N-dimethylaniline as a colorless liquid: NMR ( $CDCl_3$ )  $\delta$  2.79 (s, 6H), 6.92 (d,  $J$  = 9 Hz, 1H), 7.25-7.34 (m, 1H), 7.49 (d,  $J$  = 2 Hz, 1H).

Step 2: Preparation of 3-chloro-4-(N,N-dimethylamino)phenylboronic acid

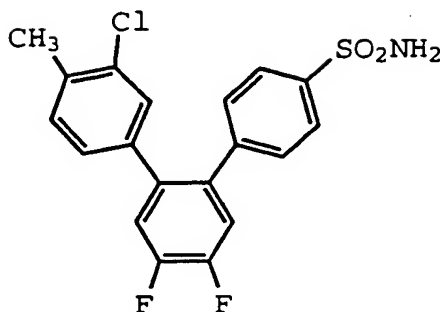
Following the general procedure outlined in Synthetic Scheme I, 11.3 g (48.2 mmol) of 4-bromo-2-chloro-N,N-dimethylaniline (Step 1) was converted to 3-chloro-4-(N,N-dimethylamino)phenylboronic acid as a colorless solid: NMR ( $CDCl_3$ )  $\delta$  2.93 (s, 6H), 7.12 (d,  $J$  = 8 Hz, 1H), 8.01 (d,  $J$  = 8 Hz, 1H), 8.12 (s, 1H).

Step 3: Preparation of 2-chloro-4-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-N,N-dimethylaniline

Following the general procedure outlined in Synthetic Scheme VI, 2.25 g (6.48 mmol) of 1-bromo-4,5-difluoro-2-[4-

(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 1.68 g (8.42 mmol) of 3-chloro-4-(N,N-dimethylamino)phenylboronic acid (Step 2). Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 2.65 g (97%) of 2-chloro-4-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]phenyl]-N,N-dimethylbenzenamine as a colorless solid: mp 129.0-130.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.81 (s, 6H), 3.05 (s, 3H), 6.76-6.91 (m, 2H), 7.08 (d,  $J$  = 2 Hz, 1H), 7.17-7.26 (m, 2H), 7.31 (d,  $J$  = 8.5 Hz, 2H), 7.83 (d,  $J$  = 8.5 Hz, 2H). MS (FAB): m/e 428 (M+Li). Anal. Calc'd for C<sub>21</sub>H<sub>18</sub>ClF<sub>2</sub>NO<sub>2</sub>S: C, 59.79; H, 4.30; N, 3.32. Found: C, 59.40; H, 4.29; N, 3.24.

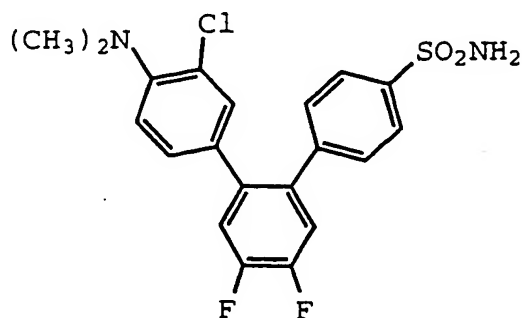
## EXAMPLE 29



5                    4-[2-(3-Chloro-4-methylphenyl)-4,5-  
                      difluorophenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 2.54 g (6.47 mmol) of 1-(3-chloro-4-methylphenyl)-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (the title compound of Example 27) was converted to its corresponding sulfonamide. Purification by silica gel chromatography (MPLC) with ethyl acetate/ hexane (1:5) gave 1.80 g (71%) of 4-[2-(3-chloro-4-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 139.0-140.0 °C; NMR (CDCl<sub>3</sub>) δ 2.33 (s, 3H), 4.81 (s, 2H), 6.74 (dd,  $J = 2, 8$  Hz, 1H), 7.04 (d,  $J = 8$  Hz, 1H), 7.12 (d,  $J = 2$  Hz, 1H), 7.17-7.25 (m, 4H), 7.80 (d,  $J = 8$  Hz, 2H). MS (FAB): m/e 400 (M+Li). Anal. Calc'd for C<sub>19</sub>H<sub>14</sub>F<sub>2</sub>ClNO<sub>2</sub>S: C, 57.95; H, 3.58; N, 3.56. Found: C, 57.91; H, 3.55; N, 3.54.

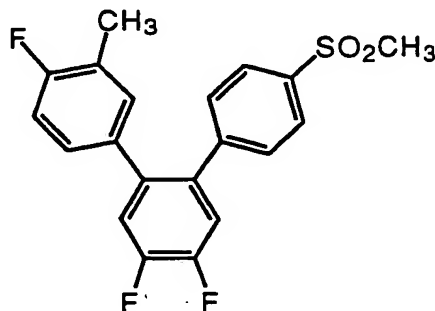
## EXAMPLE 30



**4-[2-[3-Chloro-4-(N,N-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide**

- 5        Following the general procedure outlined in Synthetic Scheme XI, 2.50 g (5.93 mmol) of 2-chloro-4-[4,5-difluoro-2-[4-(methylsulfonyl) phenyl]phenyl]-N,N-dimethylbenzenamine (the title compound of Example 28) was converted to its corresponding sulfonamide.
- 10      Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 1.75 g (70%) of 4-[2-[3-chloro-4-(N,N-dimethylamino)phenyl]-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 193.0-194.0 °C; NMR (CDCl<sub>3</sub>) δ 2.83 (s, 6H), 4.80 (s, 2H), 6.79 (dd, J = 2, 9 Hz, 1H), 6.87-6.95 (m, 1H), 7.13 (d, J = 2 Hz, 1H), 7.17-7.29 (m, 4H), 7.82 (d, J = 8 Hz, 2H). MS (FAB): m/e 429 (M+Li). Anal. Calc'd for C<sub>20</sub>H<sub>17</sub>ClF<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S (0.27 H<sub>2</sub>O): C, 56.16; H, 4.13; N, 6.55. Found: C, 56.16; H, 4.02; N, 6.39.

**EXAMPLE 31**



- 25      **1,2-Difluoro-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene**

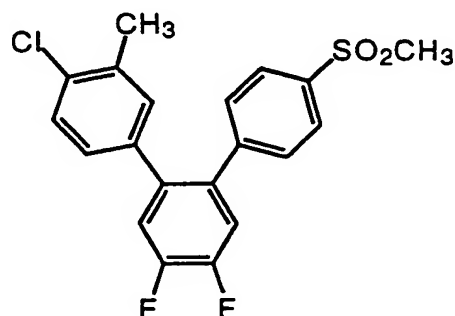
Step 1: Preparation of 4-fluoro-3-methylphenylboronic acid

Following the general procedure outlined in Synthetic Scheme I, 5-bromo-2-fluorotoluene was converted to 4-fluoro-3-methylphenylboronic acid: NMR ( $\text{CDCl}_3$ )  $\delta$  2.39 (d,  $J = 2$  Hz, 3H), 7.13 (t,  $J = 9$  Hz, 1H), 7.99-8.08 (m, 2H).

Step 2: Preparation of 1,2-difluoro-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 4-fluoro-3-methylphenylboronic acid (Step 1) to give 1,2-difluoro-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 167.2-167.5 °C; NMR ( $\text{CDCl}_3$ )  $\delta$  2.19 (d,  $J = 2$  Hz, 3H), 3.04 (s, 3H), 6.71-6.78 (m, 1H), 6.84 (t,  $J = 9$  Hz, 1H), 6.92 (dd,  $J = 2, 8$  Hz, 1H), 7.18-7.32 (m, 4H), 7.81 (d,  $J = 8$  Hz, 2H); MS (FAB)  $m/z$  383 ( $\text{M}+\text{Li}$ )<sup>+</sup>; HRMS calc'd for  $\text{M}^+$  376.0745, found 376.0752. Anal. Calc'd for  $\text{C}_{20}\text{H}_{15}\text{F}_3\text{O}_2\text{S}$ : C, 63.82; H, 4.02; F, 15.14. Found: C, 64.00; H, 3.95; F, 14.96.

### EXAMPLE 32



4-(4-Chloro-3-methylphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene

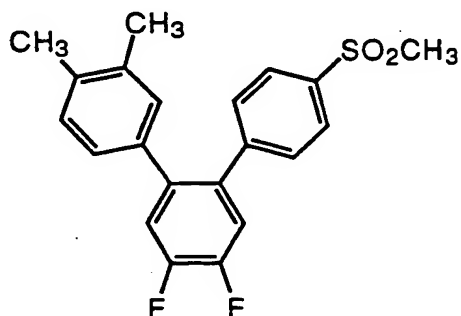
Step 1: Preparation of 4-chloro-3-methylphenylboronic

acid

Following the general procedure outlined in Synthetic Scheme I, 5-bromo-2-chlorotoluene was converted to 4-chloro-3-methylphenylboronic acid: NMR (DMSO- $d_6$ )  $\delta$  2.31 (s, 3H), 7.35 (d,  $J$  = 8 Hz, 1H), 7.59 (d,  $J$  = 8 Hz, 1H), 7.71 (s, 1H), 8.10 (br s, 2H).

Step 2: Preparation of 4-(4-chloro-3-methylphenyl)-1,2-difluoro-5-[4-(methanesulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 1-bromo-4,5-difluoro-2-[4-(methanesulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 4-chloro-3-methylphenylboronic acid (Step 1) to give 4-(4-chloro-3-methylphenyl)-1,2-difluoro-5-[4-(methanesulfonyl)phenyl]benzene as a colorless solid: mp 151.5-152.2 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.29 (s, 3H), 3.05 (s, 3H), 6.73 (dd,  $J$  = 2, 8 Hz, 1H), 6.98 (d,  $J$  = 2 Hz, 2H), 7.16 (d,  $J$  = 9 Hz, 1H), 7.19-7.32 (m, 4H), 7.82 (d,  $J$  = 9 Hz, 2H); MS (FAB)  $m/z$  399 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 392.0449, found 392.0437. Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>ClF<sub>2</sub>O<sub>2</sub>S: C, 61.15; H, 3.85; F, 9.67. Found: C, 61.04; H, 3.79; F, 9.55.

**EXAMPLE 33**

**1,2-Difluoro-4-(3,4-dimethylphenyl)-5-[4-(methanesulfonyl)phenyl]benzene**

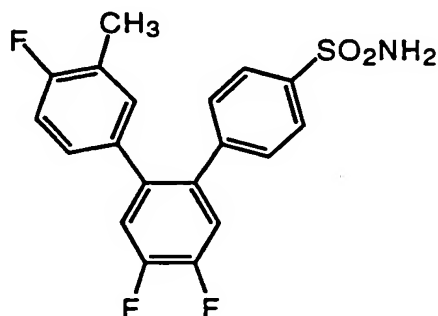
Step 1: Preparation of 3,4-dimethylphenylboronic acid

Following the general procedure outlined in Synthetic Scheme I, 4-bromo-*o*-xylene was converted to 3,4-dimethylphenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  2.19 (s, 6H), 7.07 (d,  $J$  = 8 Hz, 1H), 7.45-7.54 (m, 2H), 7.84 (br s, 2H).

Step 2: Preparation of 1,2-difluoro-4-(3,4-  
dimethylphenyl)-5-[4-  
(methylsulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 3,4-dimethylphenylboronic acid (Step 1) to give 1,2-difluoro-4-(3,4-dimethylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 125.1-125.8 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.16 (s, 3H), 2.23 (s, 3H), 3.04 (s, 3H), 6.69 (dd,  $J$  = 2, 8 Hz, 1H), 6.86 (s, 1H), 6.95 (d,  $J$  = 8 Hz, 1H), 7.16-7.26 (m, 3H), 7.29 (d,  $J$  = 9 Hz, 1H), 7.79 (d,  $J$  = 9 Hz, 2H); MS (FAB)  $m/z$  379 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 372.0996, found 372.0978. Anal. Calc'd for C<sub>20</sub>H<sub>18</sub>F<sub>2</sub>O<sub>2</sub>S: C, 67.73; H, 4.87; F, 10.20. Found: C, 67.93; H, 4.92; F, 9.82.

### EXAMPLE 34



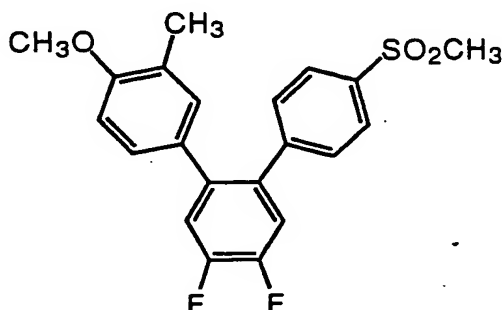
4-[4,5-Difluoro-2-(4-fluoro-3-  
methylphenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in



Synthetic Scheme XI, 1,2-difluoro-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (Example 31) was converted to 4-[4,5-difluoro-2-(4-fluoro-3-methylphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 151.5-152.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.18 (d,  $J$  = 2 Hz, 3H), 4.84 (s, 2H), 6.70-6.78 (m, 1H), 6.83 (t,  $J$  = 9 Hz, 1H), 6.94 (dd,  $J$  = 2, 8 Hz, 1H), 7.15-7.29 (m, 4H), 7.79 (d,  $J$  = 8 Hz, 2H); MS (FAB) 384 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 377.0697, found 377.0720. Anal. Calc'd for C<sub>19</sub>H<sub>14</sub>NF<sub>3</sub>O<sub>2</sub>S: C, 60.47; H, 3.74; N, 3.71. Found: C, 60.07; H, 3.84; N, 3.62.

### EXAMPLE 35



#### 1,2-Difluoro-4-(4-methoxy-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene

##### Step 1: Preparation of 4-bromo-2-methylanisole

Under nitrogen, to a stirred suspension of 38.9 g (208 mmol) of 4-bromo-2-methylphenol and 43.1 g (312 mmol) of K<sub>2</sub>CO<sub>3</sub> powder in 300 mL of THF was added 39 mL (624 mmol) of iodomethane. The mixture was heated to reflux overnight, and cooled to ambient temperature. The inorganic salts were removed by filtration, and the organic solvent was removed in vacuo. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over MgSO<sub>4</sub>. Purification by silica gel plug with ethyl acetate/hexane (5:95) gave 28 g (67%) of 4-bromo-2-methylanisole as a colorless solid: mp 65.0-66.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.18 (s, 3H), 3.80 (s,

3H), 6.67 (d,  $J$  = 9 Hz, 1H), 7.22-7.28 (m, 2H).

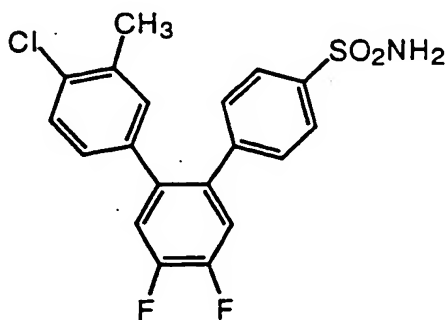
Step 2: Preparation of 4-methoxy-3-methylphenylboronic acid

Following the general procedure outlined in Synthetic Scheme I, 4-bromo-2-methylanisole was converted to 3-methyl-4-methoxyphenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  2.33 (s, 3H), 3.92 (s, 3H), 6.96 (d,  $J$  = 8 Hz, 1H), 7.98 (s, 1H), 8.03 (d,  $J$  = 8 Hz, 1H).

Step 3: Preparation of 1,2-difluoro-4-(4-methoxy-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 3-methyl-4-methoxyphenylboronic acid (Step 2) to give 1,2-difluoro-4-(4-methoxy-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 160.5-161.5 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.11 (s, 3H), 3.04 (s, 3H), 3.79 (s, 3H), 6.63 (d,  $J$  = 9 Hz, 1H), 6.74 (dd,  $J$  = 2, 9 Hz, 1H), 6.85 (d,  $J$  = 2 Hz, 1H), 7.15-7.27 (m, 3H), 7.30 (d,  $J$  = 8 Hz, 1H), 7.80 (d,  $J$  = 8 Hz, 2H); MS (FAB)  $m/z$  395 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 388.0945, found 388.0940. Anal. for C<sub>21</sub>H<sub>18</sub>F<sub>2</sub>O<sub>3</sub>S: C, 64.94; H, 4.67; F, 9.78. Found: C, 64.59; H, 4.84; F, 9.52.

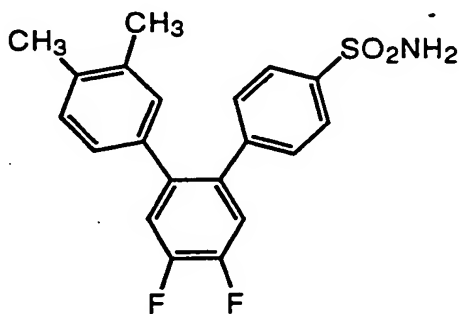
### EXAMPLE 36



**4-[2-(4-Chloro-3-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide**

Following the general procedure outlined in Synthetic Scheme XI, 4-(4-chloro-3-methylphenyl)-1,2-difluoro-5-[4-(methylsulfonyl)phenyl]benzene (Example 32) was converted to 4-[2-(4-chloro-3-methylphenyl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 141.5-142.8 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.29 (s, 3H), 4.89 (s, 2H), 6.73 (dd,  $J$  = 2, 8 Hz, 1H), 7.00 (d,  $J$  = 2 Hz, 1H), 7.15 (d,  $J$  = 8 Hz, 1H), 7.17-7.27 (m, 5H), 7.80 (d,  $J$  = 9 Hz, 1H); MS (FAB)  $m/z$  400 (M+Li)<sup>+</sup>; HRMS for M<sup>+</sup> 393.0402, found 393.0416. Anal. Calc'd for C<sub>19</sub>H<sub>14</sub>NF<sub>2</sub>ClO<sub>2</sub>S: C, 57.95; H, 3.58; N, 3.56. Found: C, 57.73; H, 3.55; N, 3.48.

**EXAMPLE 37**

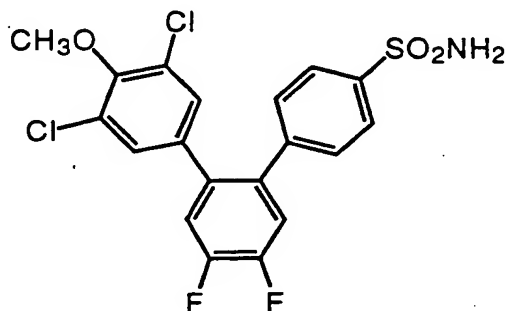


**4-[4,5-Difluoro-2-(3,4-dimethylphenyl)phenyl]benzenesulfonamide**

Following the general procedure outlined in Synthetic Scheme XI, 1,2-difluoro-4-(3,4-dimethylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (Example 33) was converted to 4-[4,5-difluoro-2-(3,4-dimethylphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 132.8-133.9 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.16 (s, 3H), 2.22 (s, 3H), 4.83 (s, 2H), 6.68 (dd,  $J$  = 2, 8 Hz, 1H), 6.88 (s, 1H), 6.94 (d,  $J$  = 8 Hz, 1H),

7.15-7.28 (m, 4H), 7.77 (d,  $J = 8$  Hz, 2H); MS (FAB)  $m/z$  380 (M+Li)<sup>+</sup>; HRMS for M<sup>+</sup> 373.0948, found 373.0972. Anal. Calc'd for C<sub>20</sub>H<sub>17</sub>NF<sub>2</sub>O<sub>2</sub>S: C, 64.33; H, 4.59; N, 3.75. Found: C, 64.20; H, 4.58; N, 3.72.

### EXAMPLE 38



#### 4-[2-(3,5-Dichloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide

##### Step 1: Preparation of 4-bromo-2,6-dichloroanisole

Following the methylation procedure described in Step 1 of Example 35, 4-bromo-2,6-dichlorophenol was methylated to give 4-bromo-2,6-dichloroanisole as a colorless solid: mp 67.0-68.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.88 (s, 3H), 7.45 (s, 2H).

##### Step 2: Preparation of 3,5-dichloro-4-methoxyphenylboronic acid

Following the general procedure outlined in Synthetic Scheme I, 4-bromo-2,6-dichloroanisole was converted to 3,5-dichloro-4-methoxyphenyl boronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  3.83 (s, 3H), 7.73 (s, 2H).

##### Step 3: Preparation of 4-(2-bromo-4,5-difluorophenyl)benzenesulfonamide

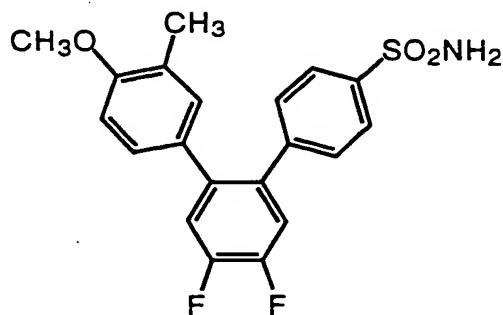
Following the general procedure outlined in Synthetic Scheme XI, 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2)

was converted to 4-(2-bromo-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: NMR (CDCl<sub>3</sub>)  $\delta$  4.87 (s, 2H), 7.12-7.21 (m, 1H), 7.49-7.58 (m, 3H), 8.00 (d,  $J$  = 9 Hz, 2H).

Step 4: Preparation of 4-[2-(3,5-dichloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme VI, 3,5-dichloro-4-methoxyphenylboronic acid (Step 2) was reacted with 4-(2-bromo-4,5-difluorophenyl]benzenesulfonamide (Step 3) to give 4-[2-(3,5-dichloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 145.5-146.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.89 (s, 3H), 4.78 (s, 2H), 6.98 (s, 2H), 7.18-7.29 (m, 4H), 7.85 (d,  $J$  = 8 Hz, 2H); MS (FAB)  $m/z$  450 (M+Li)<sup>+</sup>; HRMS calc'd for (M+H)<sup>+</sup> 444.0039, found 444.0052. Anal. Calc'd for C<sub>19</sub>H<sub>13</sub>NC<sub>12</sub>F<sub>2</sub>O<sub>3</sub>S: C, 51.37; H, 2.95; N, 3.15. Found: C, 51.59; H, 3.03; N, 3.15.

### EXAMPLE 39

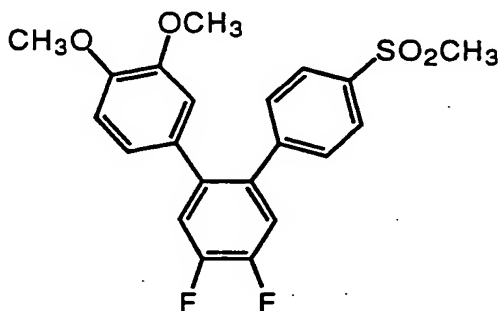


4-[4,5-Difluoro-2-(4-methoxy-3-methylphenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 1,2-difluoro-4-(4-methoxy-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (Example 35) was converted to 4-[4,5-difluoro-2-(4-

methoxy-3-methylphenyl]phenyl]benzenesulfonamide as a colorless solid: mp 120.0-121.8 °C; NMR (CDCl<sub>3</sub>)  $\delta$  2.11 (s, 3H), 3.79 (s, 3H), 4.84 (s, 2H), 6.63 (d,  $J$  = 9 Hz, 1H), 6.74 (dd,  $J$  = 2, 9 Hz, 1H), 6.88 (d,  $J$  = 2 Hz, 1H), 7.13-7.28 (m, 4H), 7.78 (d,  $J$  = 8 Hz, 2H); MS (FAB)  $m/z$  396 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 389.0897, found 389.0921. Anal. Calc'd for C<sub>20</sub>H<sub>17</sub>NF<sub>2</sub>O<sub>3</sub>S: C, 61.69; H, 4.40; N, 3.60. Found: C, 61.79; H, 4.37; N, 3.67.

### EXAMPLE 40



#### 1,2-Difluoro-4-(3,4-dimethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene

##### Step 1: Preparation of 3,4-dimethoxyphenylboronic acid

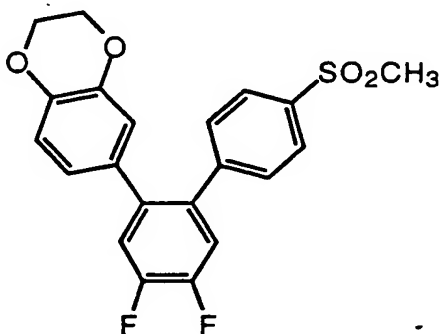
Following the general procedure outlined in Synthetic Scheme I, 1-bromo-3,4-dimethoxybenzene was converted to 3,4-dimethoxyphenylboronic acid: NMR (CDCl<sub>3</sub>)  $\delta$  3.98 (s, 3H), 4.02 (s, 3H), 7.02 (d,  $J$  = 9 Hz, 1H), 7.69 (s, 1H), 7.86 (d,  $J$  = 9 Hz, 1H).

##### Step 2: Preparation of 1,2-difluoro-4-(3,4-dimethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene

Following the general procedure outlined in Synthetic Scheme VI, 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2) was reacted with 3,4-dimethoxyphenylboronic acid (Step 1) to give 1,2-difluoro-4-(3,4-dimethoxyphenyl)-5-[4-

(methylsulfonyl)phenyl]benzene as a colorless solid: mp 140.0-141.0 °C; NMR (CDCl<sub>3</sub>) δ 3.04 (s, 3H), 3.61 (s, 3H), 3.86 (s, 3H), 6.48 (d,  $J$  = 2 Hz, 1H), 6.65 (dd,  $J$  = 2, 8 Hz, 1H), 6.75 (d,  $J$  = 8 Hz, 1H), 7.17-7.29 (m, 2H), 7.31 (d,  $J$  = 8 Hz, 2H), 7.81 (d,  $J$  = 8 Hz, 2H); MS (FAB)  $m/z$  411 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 404.0894, found 404.0893. Anal. Calc'd for C<sub>21</sub>H<sub>18</sub>F<sub>2</sub>O<sub>4</sub>S (0.24 H<sub>2</sub>O): C, 61.70; H, 4.51. Found: C, 61.69; H, 4.56.

### EXAMPLE 41



#### 6-[4,5-Difluoro-2-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1,4-benzodioxin

##### Step 1: Preparation of 2,3-dihydro-1,4-benzodioxin-6-boronic acid

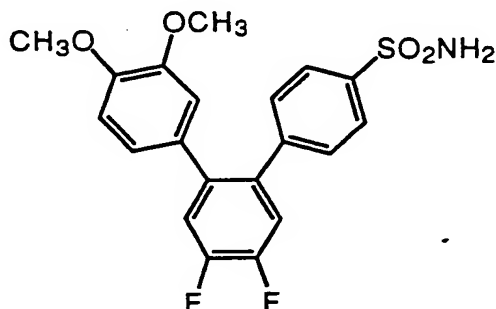
Following the general procedure outlined in Synthetic Scheme I, 3,4-ethylenedioxybromobenzene was converted to 2,3-dihydro-1,4-benzodioxin-6-boronic acid: NMR (CDCl<sub>3</sub>) δ 4.27-4.36 (m, 4H), 6.97 (d,  $J$  = 9 Hz, 1H), 7.67-7.72 (m, 2H).

##### Step 2: Preparation of 6-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1,4-benzodioxin

Following the general procedure outlined in Synthetic Scheme VI, 1-bromo-4,5-difluoro-2-[4-(methylsulfonyl)phenyl]benzene (Example 18, Step 2)

was reacted with 2,3-dihydro-1,4-benzodioxin-6-boronic acid (Step 1) to give 6-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1,4-benzodioxin as a colorless solid: mp 82.0-83.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.05 (s, 3H), 4.21-4.26 (m, 4H), 6.43 (dd,  $J$  = 2, 8 Hz, 1H), 6.61 (d,  $J$  = 2 Hz, 1H), 6.68 (d,  $J$  = 8 Hz, 1H), 7.14-7.24 (m, 2H), 7.31 (d,  $J$  = 8 Hz, 2H), 7.81 (d,  $J$  = 8 Hz, 2H); MS (FAB)  $m/z$  409 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 402.0737, found 402.0749. Anal. Calc'd for C<sub>21</sub>H<sub>16</sub>F<sub>2</sub>O<sub>4</sub>S (0.17 hexane): C, 63.41; H, 4.44. Found: C, 63.50; H, 4.28.

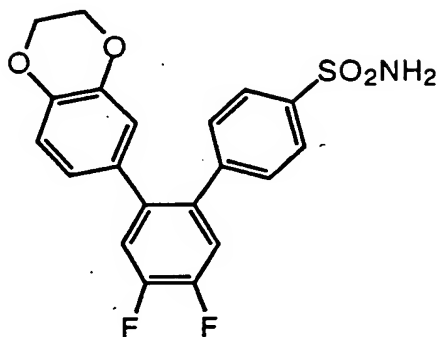
## EXAMPLE 42



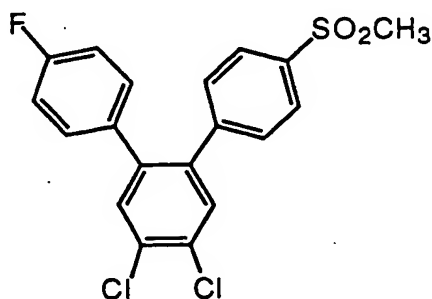
### 4-[4,5-Difluoro-2-(3,4-dimethoxyphenyl)phenyl]benzenesulfonamide

Following the general procedure outlined in Synthetic Scheme XI, 1,2-difluoro-4-(3,4-dimethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]benzene (Example 40) was converted to 4-[4,5-difluoro-2-(3,4-dimethoxyphenyl)phenyl]benzenesulfonamide as a colorless solid: mp 157.0-158.0 °C; NMR (CDCl<sub>3</sub>)  $\delta$  3.61 (s, 3H), 3.86 (s, 3H), 4.77 (s, 2H), 6.46 (d,  $J$  = 2 Hz, 1H), 6.65 (dd,  $J$  = 2, 8 Hz, 1H), 6.75 (d,  $J$  = 8 Hz, 1H), 7.16-7.30 (m, 4H), 7.79 (d,  $J$  = 8 Hz, 2H); MS (FAB)  $m/z$  412 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 405.0846, found 405.0870. Anal. Calc'd for C<sub>20</sub>H<sub>17</sub>NF<sub>2</sub>O<sub>4</sub>S (0.35 H<sub>2</sub>O): C, 58.33; H, 4.33; N, 3.40. Found: C, 58.34; H, 4.23; N, 3.31.



**EXAMPLE 43****4-[2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4,5-difluorophenyl]benzenesulfonamide**

Following the general procedure outlined in Synthetic Scheme XI, 6-[4,5-difluoro-2-[4-(methylsulfonyl)phenyl]-2,3-dihydro-1,4-benzodioxin (Example 41) was converted to 4-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,5-difluorophenyl]benzenesulfonamide as a colorless solid: mp 107.0-108.0 °C; NMR (CDCl<sub>3</sub>) δ 4.22-4.26 (m, 4H), 4.75 (s, 2H), 6.43 (dd,  $J = 2, 8$  Hz, 1H), 6.62 (d,  $J = 2$  Hz, 1H), 6.68 (d,  $J = 8$  Hz, 1H), 7.13-7.30 (m, 4H), 7.80 (d,  $J = 8$  Hz, 2H); MS (FAB)  $m/z$  410 (M+Li)<sup>+</sup>; HRMS calc'd for M<sup>+</sup> 403.0690, found 403.0697. Anal. Calc'd for C<sub>20</sub>H<sub>15</sub>NO<sub>4</sub>F<sub>2</sub>S: C, 59.55; H, 3.75; N, 3.47. Found: C, 59.89; H, 3.99; N, 3.20.

**EXAMPLE 44**

**1,2-Dichloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene**

**Step 1: Preparation of benzyltrimethylammonium tetrachloroiodate**

Following Kajigaeshi's procedure [Tetrahedron Lett., 29, 7201-7204, (1988)], 18.6 g (100 mmol) of benzyltrimethylammonium chloride was added to a stirred solution of 23.3 g (100 mmol) of  $\text{ICl}_3$  in 300 mL of  $\text{CH}_2\text{Cl}_2$ . The product was collected and dried in vacuo to give 38.4 g (92%) of benzyltrimethylammonium tetrachloroiodate as a bright yellow solid: mp 105.5-127.5 °C.

**Step 2: Preparation of 1,2-dichloro-4,5-dimethoxybenzene**

Following Kajigaeshi's procedure [Chem. Lett., 415-418, (1989)], 38 g (91 mmol) of benzyltrimethylammonium tetrachloroiodate (Step 1) was added to a stirred solution of 6.3 g (45.5 mmol) of 1,2-dimethoxybenzene in 100 mL of HOAc, and the reaction was stirred for 2 hours at ambient temperature. Concentration in vacuo gave a residue, which was dissolved in toluene. The resulting solution was washed with aqueous  $\text{Na}_2\text{SO}_3$  and dried over  $\text{MgSO}_4$ . Recrystallization from hexane gave 6.0 g (64%) of 1,2-dichloro-4,5-dimethoxybenzene as a colorless solid: mp 81.0-82.5 °C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.86 (s, 6H), 6.91 (s, 2H).

**Step 3: Preparation of 1,2-dichlorocatechol**

Under nitrogen, 83.4 mL (83.4 mmol) of  $\text{BBr}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ ) was added at 0 °C to a stirred solution of 5.75 g (27.8 mmol) of 1,2-dichloro-4,5-dimethoxybenzene (Step 2) in 200 mL of  $\text{CH}_2\text{Cl}_2$ , and the reaction was stirred for 2 hours at ambient temperature. Concentration in vacuo gave a residue, which was dissolved in ethyl acetate. The resulting

solution was washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Recrystallization from ethyl acetate/hexane (5:95) gave 5.0 g (96%) of 1,2-dichlorocatechol as a gray solid: mp 113.0-114.5 °C; NMR ( $\text{CDCl}_3$ )  $\delta$  5.18 (s, 2H), 6.98 (s, 2H).

Step 4: Preparation of 1,2-dichloro-4,5-bis(trifluoromethanesulfonyl)benzene

Under nitrogen, 8.4 mL (104 mmol) of pyridine and 9.0 mL (53.5 mmol) of triflic anhydride at 0 °C was added to a stirred solution of 3.72 g (20.8 mmol) of 1,2-dichlorocatechol (Step 3) in 40 mL of  $\text{CH}_2\text{Cl}_2$ , and the reaction was stirred for 7 days at ambient temperature. The mixture was poured into ice-water, extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined extracts were dried over  $\text{Na}_2\text{SO}_4$ . Purification by silica gel plug with ethyl acetate/hexane (5:95) gave 7.9 g (86%) of 1,2-dichloro-4,5-bis(trifluoromethanesulfonyl)benzene as a yellow oil: NMR ( $\text{CDCl}_3$ )  $\delta$  7.62 (s, 2H).

Step 5: Preparation of 1,2-dichloro-4-[4-(methylthio)phenyl]-5-(trifluoromethanesulfonyl)benzene

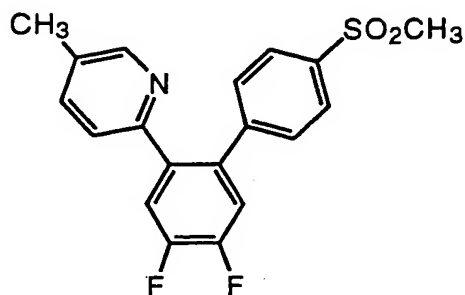
Under nitrogen, 5 g (4.3 mmol) of  $\text{Pd}(\text{PPh}_3)_4$  was added to a stirred solution of 7.9 g (17.8 mmol) of 1,2-dichloro-4,5-bis(trifluoromethanesulfonyl)benzene (Step 4), 3.0 g (18 mmol) of 4-methylthiophenylboronic acid (Example 1, Step 2) and 7.4 g (54 mmol) of anhydrous  $\text{K}_2\text{CO}_3$  powder in 90 mL of toluene. The reaction was stirred at reflux for 48 hours, and diluted with  $\text{CH}_2\text{Cl}_2$ . The resulting solution was washed with water and brine, and dried over  $\text{MgSO}_4$ . Purification by silica gel plug with ethyl acetate/hexane (5:95 to 30:70) gave 4.8 g (56%) of 1,2-dichloro-4-[4-(methylthio)phenyl]-5-(trifluoromethanesulfonyl)benzene as a colorless solid: NMR ( $\text{CDCl}_3$ )  $\delta$  2.54 (s, 3H), 7.33 (s, 4H), 7.50 (s, 1H), 7.56 (s, 1H).

Step 6: Preparation of 1,2-dichloro-4-(4-fluorophenyl)-

5-[4-(methylsulfonyl)phenyl]benzene

Under nitrogen, 480 mg (0.42 mmol) of  $\text{Pd}(\text{PPh}_3)_4$  was added to a stirred solution of 1.64 g (3.93 mmol) of 1,2-dichloro-4-[4-(methylthio)phenyl]-5-(trifluoromethanesulfonyl)benzene (Step 5), 1.1 g (7.9 mmol) of 4-fluorophenylboronic acid and 1.6 g (11.6 mmol) of anhydrous  $\text{K}_2\text{CO}_3$  powder in 20 mL of toluene. The reaction was vigorously stirred at reflux for 7 days, and cooled to ambient temperature. The reaction mixture was diluted with ethyl acetate. The resulting solution was washed with water, and dried over  $\text{MgSO}_4$ . Purification by silica gel plug with ethyl acetate/hexane (5:95) gave an oil residue which was subsequently dissolved in 15 mL of  $\text{CH}_2\text{Cl}_2$ . The resulting solution was treated with 1.4 g (11.8 mmol) of 3-chloroperbenzoic acid (MCPBA) (70%) at 0 °C; and the reaction was stirred overnight at ambient temperature. Excess MCPBA was quenched by the addition of  $\text{Na}_2\text{SO}_3$  at 0 °C, and stirred for 30 minutes at ambient temperature. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$ , the resulting solution was washed with water and brine, and dried over  $\text{Na}_2\text{SO}_4$ . Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (3:7) gave 505 mg (33%) of 1,2-dichloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]benzene as a colorless solid: mp 143.5-144.5 °C; NMR ( $\text{CDCl}_3$ )  $\delta$  3.05 (s, 3H), 6.95 (d,  $J$  = 9 Hz, 2H), 6.99-7.07 (m, 2H), 7.30 (d,  $J$  = 9 Hz, 2H), 7.52 (d,  $J$  = 9 Hz, 2H), 7.83 (d,  $J$  = 9 Hz, 2H); MS (CI)  $m/z$  395 ( $\text{M}+\text{H}$ )<sup>+</sup>; HRMS calc'd for ( $\text{M}+\text{Li}$ )<sup>+</sup> 401.0157, found 401.0142. Anal. Calc'd for  $\text{C}_{19}\text{H}_{13}\text{O}_2\text{SFCl}_2$ : C, 57.73; H, 3.31; F, 4.81; Cl, 17.94. Found: C, 57.89; H, 3.45; F, 4.81; Cl, 17.56.

## EXAMPLE 45



2-[4,5-Difluoro-4'-(methylsulfonyl)-(1,1'-  
biphenyl)-2-yl]-5-methylpyridine

Step 1: Preparation of 4,5-difluoro-2-[(4-methylthio)phenyl]phenylboronic acid

Under nitrogen, 1 mL of dibromoethane was added to a mixture of 3.87 g (12.3 mmol) of 1-bromo-4,5-difluoro-2-[4-(methylthio)phenyl]benzene (Example 18, Step 1) and 300 mg (12.3 mmol) of magnesium turnings in 12 mL of anhydrous THF. The reaction was heated to reflux for 5 hours, cooled to 0 °C, treated with 2.8 mL (24.6 mmol) of trimethylborate, and stirred overnight. After 10 mL of 10% NaOH was added, the solution was stirred for 3 hours, acidified to pH 4, and extracted with ethyl acetate three times. The combined extracts were dried over MgSO<sub>4</sub> and concentrated in vacuo to give 2.7 g (78%) of 4,5-difluoro-2-[(4-methylthio)phenyl]phenylboronic acid as a pale yellow semi-solid.

Step 2: Preparation of 2-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-5-methylpyridine

Under nitrogen, 1 g (0.86 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub> was added to a stirred solution of 2.7 g (9.6 mmol) of 4,5-difluoro-2-[(4-methylthio)phenyl]phenylboronic acid (Step 1) and 1.7 g (9.8 mmol) of 2-bromo-5-methylpyridine in a mixed solvent of 25 mL of toluene,

25 mL of ethanol and 25 mL of 2M  $\text{Na}_2\text{CO}_3$ . The reaction was stirred at reflux for 48 hours, and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, and the resulting solution was washed with water and brine, and dried over  $\text{Na}_2\text{SO}_4$ .

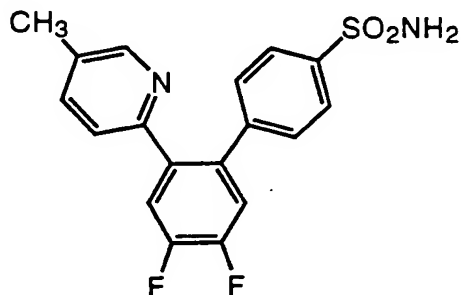
Purification by silica gel plug with ethyl acetate/hexane (15:85) gave a semi-solid residue which was then dissolved in a mixed solvent of 15 mL of THF and 15 mL of  $\text{CH}_3\text{OH}$ . A solution of 3.5 g (5.7 mmol) of potassium peroxymonosulfate (OXONE®) in 15 mL of  $\text{H}_2\text{O}$  was slowly added, and the stirring was continued for 3 hours at ambient temperature. Excess OXONE® was destroyed by the addition of 2 g of  $\text{Na}_2\text{SO}_3$ .

Concentrated in vacuo gave a residue which was dissolved in ethyl acetate; and the resulting solution was washed with brine, and dried over  $\text{Na}_2\text{SO}_4$ .

Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (45:55) gave 1.0 g (29%) of 2-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-5-methylpyridine as a colorless foam: NMR ( $\text{CDCl}_3$ )  $\delta$  2.32 (s, 3H), 3.05 (s, 3H), 6.76 (d,  $J$  = 8 Hz, 1H), 7.17-7.36 (m, 4H), 7.53 (t,  $J$  = 9 Hz, 1H), 7.82 (d,  $J$  = 9 Hz, 2H), 8.42 (s, 1H); MS (FAB)  $m/z$  360 ( $M+H$ )<sup>+</sup>; HRMS calc'd for ( $M+H$ )<sup>+</sup> 360.0870, found 360.0885.

Anal. Calc'd for  $\text{C}_{19}\text{H}_{15}\text{NO}_2\text{SF}_2$ : C, 63.50; H, 4.21; N, 3.90; F, 10.57. Found: C, 63.28; H, 4.30; N, 3.65; F, 10.24.

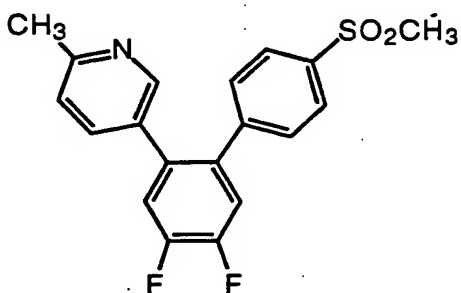
## EXAMPLE 46



**4-[4,5-Difluoro-2-(5-methylpyridin-2-yl)phenyl]benzenesulfonamide**

Following the general procedure outlined in Synthetic Scheme XI, 2-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-5-methylpyridine (Example 45) was converted to 4-[4,5-difluoro-2-(5-methylpyridin-2-yl)phenyl]benzenesulfonamide as a colorless foam: NMR (CDCl<sub>3</sub>)  $\delta$  2.55 (s, 3H), 4.91 (s, 2H), 6.81 (d, J = 8 Hz, 1H), 7.18-7.31 (m, 3H), 7.35 (d, J = 8 Hz, 1H), 7.50-7.59 (m, 1H), 7.82 (d, J = 9 Hz, 2H), 8.47 (s, 1H); MS (FAB) m/z 361 (M+H)<sup>+</sup>; HRMS calc'd for (M+Li)<sup>+</sup> 367.0904, found 367.0904. Anal. Calc'd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>SF<sub>2</sub> (0.13 hexane): C, 60.73; H, 4.30; N, 7.13. Found: C, 60.47; H, 4.54; N, 7.13.

**EXAMPLE 47**



**5-[4,5-Difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-2-methylpyridine**

Step 1: Preparation of 5-bromo-2-methylpyridine

Following Reitz's procedure [U.S. Patent No. 5,155,177], under nitrogen, 12.3 mL (238 mmol) of bromine was slowly added at 100 °C to a stirred suspension of 76.6 g (576 mmol) of AlCl<sub>3</sub> in 23.7 mL (240 mmol) of 2-methylpyridine. The reaction was heated at 100 °C overnight, cooled to ambient

temperature, and slowly poured into ice water. Aqueous  $\text{Na}_2\text{SO}_3$  was added to destroy excess bromine, followed by 50% aqueous  $\text{NaOH}$  to dissolve the aluminum salts. The mixture was extracted with ethyl ether (3 X) and dried over  $\text{MgSO}_4$ . Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (15:85) gave 8.6 g (21%) of 5-bromo-2-methylpyridine as a pale brown oil: NMR ( $\text{CDCl}_3$ )  $\delta$  2.48 (s, 3H), 7.02 (d,  $J$  = 9 Hz, 1H), 7.65 (dd,  $J$  = 2, 9 Hz, 1H), 8.52 (d,  $J$  = 2 Hz, 1H).

Step 2: Preparation of 2-methyl-5-(trimethyltin)pyridine

Under nitrogen, 14 mL (35 mmol) of *n*-butyllithium (2.5 M in hexanes) was added to a stirred solution of 5.2 g (30 mmol) of 5-bromo-2-methylpyridine (Step 1) in 300 mL of anhydrous THF at  $-78^\circ\text{C}$ . After 10 minutes, a solution of 7.2 g (36 mmol) of trimethyltin chloride in 5 mL of anhydrous THF was added. The reaction was warmed to ambient temperature, and stirred overnight. Concentration in vacuo gave a residue, which was dissolved in ethyl acetate. The resulting solution was washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Purification by silica gel chromatography (Waters PrepLC 500A) with ethyl acetate/hexane (1:3) gave 2.0 g (29%) of 2-methyl-5-(trimethyltin)pyridine as a yellow oil: NMR ( $\text{CDCl}_3$ )  $\delta$  0.31 (s, 9H), 2.52 (s, 3H), 7.11 (d,  $J$  = 8 Hz, 1H), 7.65 (dd,  $J$  = 2, 8 Hz, 1H), 8.49 (s, 1H).

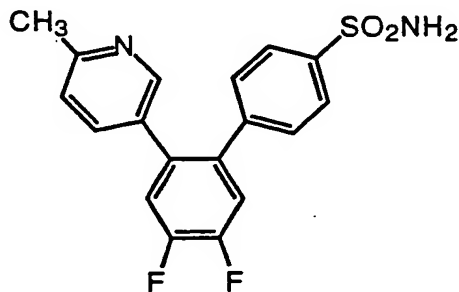
Step 3: Preparation of 5-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-2-methylpyridine

Under nitrogen, 100 mg (0.1 mmol) of  $\text{Pd}(\text{PPh}_3)_4$  was added to a stirred solution of 200 mg (0.6 mmol) of 1-bromo-4,5-difluoro-2-[(4-methylsulfonyl)phenyl]benzene (Example 18, Step 2) and 300 mg (1.2 mmol) of 2-methyl-5-(trimethyltin)pyridine



(Step 2) in 5 mL of toluene. The reaction was stirred at reflux for 16 hours, and cooled to ambient temperature. Concentration in vacuo gave a residue which was dissolved in ethyl acetate. The resulting solution was washed with water and brine, and dried over  $\text{Na}_2\text{SO}_4$ . Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:1) gave 70 mg (32%) of 5-[4,5-difluoro-4'-(methylsulfonyl)-(1,1'-biphenyl)-2-yl]-2-methylpyridine as a pale brown solid: mp 141.0-142.5 °C; NMR ( $\text{CDCl}_3$ )  $\delta$  2.52 (s, 3H), 3.04 (s, 3H), 7.02 (d,  $J$  = 8 Hz, 1H), 7.19-7.32 (m, 5H), 7.82 (d,  $J$  = 8 Hz, 2H), 8.24 (s, 1H); MS (FAB)  $m/z$  360 ( $\text{M}+\text{H}$ )<sup>+</sup>; HRMS calc'd for ( $\text{M}+\text{H}$ )<sup>+</sup> 360.0870, found 360.0862. Anal. Calc'd for  $\text{C}_{19}\text{H}_{15}\text{NO}_2\text{SF}_2$  (0.33  $\text{H}_2\text{O}$ ): C, 62.45; H, 4.24; N, 3.84. Found: C, 62.46; H, 4.32; N, 3.83.

### EXAMPLE 48



#### 4-[4,5-Difluoro-2-(6-methylpyridin-3-yl)phenyl]benzenesulfonamide

Under nitrogen, 150 mg of  $\text{Pd}(\text{PPh}_3)_4$  was added to a stirred solution of 800 mg (2.3 mmol) of 4-(2-bromo-4,5-difluorophenyl)benzenesulfonamide (Example 38, Step 3) and 1.0 g (4.6 mmol) of 2-methyl-5-(trimethyltin)pyridine (Example 47, Step 2) in 20 mL of toluene. The reaction was stirred at reflux for 16 hours, and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate; and the

resulting solution was washed with water and brine, and dried over  $\text{MgSO}_4$ . Purification by silica gel chromatography (MPLC) with ethyl acetate/hexane (1:1) followed by reverse phase chromatography (Waters Delta Prep) gave 540 mg (65%) of 4-[4,5-difluoro-2-(6-methylpyridin-3-yl)phenyl]benzenesulfonamide as a colorless solid: mp > 96 °C (dec); NMR ( $\text{CDCl}_3$ )  $\delta$  2.55 (s, 3H), 5.10 (s, 2H), 7.09 (d,  $J$  = 8 Hz, 1H), 7.20-7.28 (m, 4H), 7.32 (dd,  $J$  = 2, 9 Hz, 1H), 7.81 (d,  $J$  = 9 Hz, 2H), 8.21 (d,  $J$  = 2 Hz, 1H); MS (FAB)  $m/z$  361 ( $M+H$ )<sup>+</sup>; HRMS calc'd for ( $M+H$ )<sup>+</sup> 361.0822, found 361.0823. Anal. Calc'd for  $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2\text{SF}_2$ : C, 59.99; H, 3.92; N, 7.77; F, 10.54. Found: C, 59.72; H, 4.05; N, 7.64; F, 10.46.

#### BIOLOGICAL EVALUATION

##### Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and

Bliven, *Laboratory Models for Testing NSAIDs*, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

#### Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table I.

TABLE I.

Examples	RAT PAW EDEMA	ANALGESIA
	% Inhibition	% Inhibition
	@ 10mg/kg body weight	@30mg/kg body weight
1	26	ND
2	6	28
3	14	1
20	19	22*
* Assay performed at 50 mg/kg body weight		

### Evaluation of COX I and COX II activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX II. The COX II inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

#### a. Preparation of recombinant COX baculoviruses

A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamHI site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ( $2 \times 10^8$ ) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer ( $10^7$ - $10^8$  pfu/ml) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors ( $0.5 \times 10^6$ /ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

#### b. Assay for COX-1 and COX-2 activity:

COX activity was assayed as PGE<sub>2</sub> formed/µg

protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10  $\mu$ M). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37 °C/room temperature by transferring 40  $\mu$ l of reaction mix into 160  $\mu$ l ELISA buffer and 25  $\mu$ M indomethacin. The PGE<sub>2</sub> formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II.

Example	Human COX-2	Human COX-1
	ID <sub>50</sub> $\mu$ M	ID <sub>50</sub> $\mu$ M
1	0.3	>100
2	<0.1	19
3	<0.1	3.9
4	2.6	>100
5	11.4	>100
6	<0.1	13.1
7	<0.1	8.2
8	0.1	>100
9	2.8	32.6
10	0.4	>100
11	<0.1	>100
12	<0.1	9.2
13	<0.1	5.7
14	<0.1	>100
15	7.2	>100
16	<0.1	5.5
17	<0.1	>100
18	<0.1	>100
19	<0.1	>100
20	<0.1	18.9

TABLE II. (cont.)

Example	Human COX-2	Human COX-1
	ID <sub>50</sub> $\mu$ M	ID <sub>50</sub> $\mu$ M
21	<0.1	22.5
22	<0.1	5.3
23	<0.1	>100
24	<0.1	>100
25	<0.1	17.0
26	<0.1	1.7
27	<0.1	>100
28	<0.1	>100
29	<0.1	16.5
30	<0.1	0.6
31	<0.1	>100
32	<0.1	>100
33	<0.1	>100
34	<0.1	3.7
35	<0.1	>100
36	<0.1	3.9
37	<0.1	14.6
38	<0.1	>100
39	<0.1	10.9
40	0.3	>100
42	<0.1	>100
43	<0.1	17.9
45	52.3	>100
46	0.3	>100
47	0.2	>100
48	<0.1	>100

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this combination therapy in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier"

materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical

preparation of compounds of this invention to the affected area two to four times a day.

For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known



manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active

ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.